PART II: HIV-1 CTL EPITOPES

SUMMARY

Part II includes tables, maps, and associated references of HIV-specific CTL epitopes arranged sequentially according to the location of the proteins in the HIV-1 genome. We attempted to make this section as comprehensive as possible, requiring that the epitope be contained within a defined region of a maximum of 30 amino acids, but not that the precise boundaries be defined. Studies that were based on the analysis of whole proteins are described at the end of each protein section. The same epitope can have multiple entries, and each entry represents a single publication in this section of the database. For more recent updates and useful searching capabilities, please see our web site: http://hiv-web.lanl.gov/immunology. For a concise listing of the best defined CTL epitopes, see the summary by Christian Brander and Philip Goulder in Part I of this compendium. CTL protein reactions with no well-defined epitopes are listed at the end of each protein section.

A. CTL EPITOPE TABLES

Each CTL reference has a six part basic entry:

- **HXB2 Location:** The viral strain HXB2 (GenBank Accession Number K03455) is used as a reference strain throughout this publication. The position of the defined epitope location on the sequence of the HXB2 protein is indicated. Obviously HXB2 may not be identical to a given defined reactive sequence, so we are simply indicating the location of the aligned positions. The HXB2 numbering is used in the protein maps in this database and is the reference strain in the HIV Sequence Compendium. HXB2 was chosen as the reference clone because it is the most intensively studied strain in terms of immunogenecity, structure, and function.
- **Author Location:** The amino acid positions of the epitope boundaries and the reference sequence are listed as given in the primary publication. Frequently, these positions as published are imprecise, and do not truly correspond to the numbering of the sequence, but they provide a reasonable guide to the peptide's approximate location in the protein. Also, in many cases the reference sequence identification was not provided, and in such cases it is not possible to use these numbers to specify precise locations. If you are interested in finding the precise positions of epitopes you are studying relative to the HXB2 strain, please try using the interactive position locator at our web site: http://hiv-web.lanl.gov/NUM-HXB2/HXB2.MAIN.html.
- **Epitope Sequence:** The amino acid sequence of the epitope of interest as defined in the reference, based on the reference strain used in the study defining the epitope. On rare occasions, when only the epitope location and not the actual epitope sequence was specified in the original publication, and the sequences were numbered inaccurately by the primary authors, we may have misrepresented the epitope's amino acid sequence. Therefore epitopes that were not explicitly written out in the text in the primary publication, those that we determined by looking up the reference strain and the numbered location, are followed by a question mark in the table.
- **Immunogen:** The antigenic stimulus of the CTL response.
- **Species(HLA):** The species responding and HLA of MHC specificity of the epitope.
- **Reference:** The primary reference (sometimes two or more directly related studies are included).

Following the entry for a given CTL epitope are brief comments explaining the context in which the epitope was studied. If the same epitope was studied in several labs, each study is cited in its own bulleted entry.

B. HIV PROTEIN EPITOPE MAPS

Because of the increasing number of defined epitopes, only HIV CTL epitopes and mapped to within a region of 21 amino acids or less, with a known HLA specificity, are indicated on the HIV protein epitope maps.

The location and HLA restriction elements of CTL epitopes are indicated on protein sequences of HXB2. These maps are meant to provide the relative location of epitopes on a given protein, but the HXB2 sequence may not actually carry the epitope of interest, as it may vary relative to the sequence for which the epitope was defined. Epitopes are numbered in bold on the maps; the map numbering corresponding to the numbering of the epitope sequence alignments.

C. REFERENCES AND NOTES

ALIGNMENTS

To conserve space, no epitope alignments are provided in this book, but they can be generated using the CTL epitope search tool at

`http://hiv-web.lanl.gov/immunology`

Part II-A: Table of CTL Epitopes

All CTL epitopes arranged by protein position

Table 1: **p17**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
p17(11–19)	Gag(11–19 HXB2)	GELDRWEKI	HIV-1 infection	human(B*4002)	[Mulligan (2001)]
• Epitope G2 from Patient 12129 with HLA genotypes A*0207, A*0217, B*0801, B*4002, Cw*0303, Cw*07(01, 06)					
p17(18–26)	p17(18–26 IIIB)	KIRLRPGGK		human(A*0301)	[Brander & Goulder(2001)]
• C. Brander notes that this is an A*0301 epitope					
p17(18–26)	p17(18–26 SF2)	KIRLRPGGK	HIV-1 infection	human(A*0301)	[Altfeld (2001a)]
• HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from seven proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study					
• The reactive peptide p17 gag WEKIRLRPGGKKKYK contained two A*0301-restricted epitopes, KIRLRPGGK and RLRPGGKKK					
p17(18–26)	p17(18–26 IIIB)	KIRLRPGGK	HIV-1 infection	human(A3)	[Wilson (1996)]
• Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study					
• KIRLRPGGR and RIRLRPGGR, naturally occurring variants, were found in the mother, and are escape mutants					
p17(18–26)	p17(18–26)	KIRLRPGGK	*in vitro* stimulation	human(A3)	[Zarling (1999)]
• This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses					
• Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA					
• A weak response to KLTPLCVSL was stimulated using macrophages as the APC					
• No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL					
p17(18–26)	Gag(18–26)	KIRLRPGGK	HIV-1 infection	human(A3)	[Brodie (1999)]
• CTL effector cells were studied by expanding autologous HIV-1 Gag-specific CTL *in vitro*, and adoptive transfer					
• The transferred CTLs migrated to the lymph nodes and transiently reduced circulating productively-infected CD4+ T-cells, showing that CTL move to appropriate target sites and mediate anti-viral effects					
p17(18–26)	(18–26)	KIRLRPGGK	HIV-1 infection	human(A3)	[Brodie (2000)]
• Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL					
• Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, co-localizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication					
• The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1α and MIP-1β, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism					

- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*

p17(18–26)	p17(18–26 IIIB)	KIRLRPGGK	HIV-1 infection	SJL/J HLA transgenic mice(A3)	[Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- KIRLRPGGR and RIRLRPGGR were escape mutants
- This epitope was recognized and many escape mutants were detected in an HLA A3 transmitting mother, and was recognized but invariant in an HLA A3 non-transmitting mother

p17(18–26)	p17(18–26 IIIB)	KIRLRPGGK	HIV-1 infection	human(A3)	[Goulder (1997e), Goulder (1997a)]

- Identical twin hemophiliac brothers were both infected with the same batch of factor VIII. One had a response to this epitope, the other did not. [Goulder (1997e)] is a review of immune escape that summarizes this study.

p17(18–26)	p17( )	KIRLRPGGK	HIV-1 exposed seronegative	human(A3)	[Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells
- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women

p17(18–26)	p17( )	KIRLRPGGK	HIV-1 infection	human(A3)	[Goulder (2000a)]

- WEKIRLRPGGKKKYKLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – 7/10 that had a dominant response to this epitope were A3, and 5/7 targeted RLRPGGKKK while 2/7 targeted KIRLRPGGK (this tally comes from the tables, not the text of the paper)
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

p17(18–26)	p17( )	KIRLRPGGK	HIV-1 infection	human(A3)	[Seth (2001)]

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized

p17(18–26)	p17(18–26 SF2)	KIRLRPGGK	HIV-1 infection	human(A3)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 3/7 group 1, 0/4 group 2, and 2/2 group 3

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p17(18–26)	p17(18–26)	KIRLRPGGK	HIV-1 exposed seronegative, HIV-1 infection	human(A3)	[Kaul (2001a)]

- KIRLRPGGK is cross-reactive for A, B, and D clades
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

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p17(18–26)	p17( )	KIRLRPGGK	HIV-1 infection	human(A3)	[Severino (2000)]

- Primary HLA-A3+ CD4+ and HLA-mismatched lymphocytes from uninfected donors were infected with JRCSF after isolation then cocultured with the A3-restricted CTL clone 11504/A7 specific for KIRLRPGGK, and viral inhibition was MHC-restricted
- Primary monocytes and monocyte-derived DC were generated from the same donors, replication of HIV-1 in these cell types was less efficient than in lymphocytes and could also be inhibited by MHC-restricted CTL
- DC-lymphocyte cluster cultures allowed vigorous viral replication and MHC-restricted CTL viral inhibition was blunted or lost depending on the ratio of DC to CD4+ lymphocyte in the culture

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p17(18–26)	p17(18–26)	KIRLRPGGK	HIV-1 infection	human(A3)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant

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p17(18–26)	p17(18–26)	KIRLRPGGK	HIV-1 infection	human(A3)	[Ostrowski (2000)]

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T-cell help in 9/10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T-cell help to a variable degree in most of patients
- Those CTL that didn't respond to CD40LT could expand with IL-2 present, and IL-15 produced by dendritic cells also contributes
- The T-helper epitope used for CD4+ T-cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKANSKFIGITE)

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p17(18–26)	p17(18–26)	KIRLRPGGK	HIV-1 infection	human(A3, A3.1, B27)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

p17(18–26)	( )	KIRLRPGGK	HIV-1 infection	human(B*0301)	[Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

p17(18–27)	p17(18–27 LAI)	KIRLRPGGKK		human(B27)	[Brander & Walker(1996)]

- D. Lewinsohn, pers. comm.

p17(18–27)	p17(18–27)	KIRLRPGGKK	HIV-1 infection	human(B27)	[Birk (1998)]

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs

p17(18–31)	p17(18–31)	KIRLRPGGKKKYKL	HIV-1 infection	human(A3)	[Birk (1998)]

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs

p17(18–31)	p17(18–31)	KIRLRPGGKKKYKL	HIV-1 infection	human(B62)	[Lubaki (1997)]

- Eighty-two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of CTL response
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response
- A subject who was HLA-B62+ had CTL that recognized this peptide, and p24 LGLNKIVRMYS, and one additional unknown epitope

p17(18–42)	p17(18–42 IIIB)	KIRLRPGGKKKYKLK-HIVWASRELE	HIV-1 infection	human(A3)	[Jassoy (1992)]

- Epitope recognized by CTL clone derived from CSF

p17(18–42)	p17(18–42 PV22)	KIRLRPGGKKKYKLK-HIVWASRELE	HIV-1 infection	human(A3)	[Jassoy (1993)]
	• HIV-1 specific CTLs release γ-IFN, and α- and β-TNF				
p17(18–42)	p17(18–42 BH10)	KIRLRPGGKKKYKLK-HIVWASRELE	HIV-1 infection	human(Bw62)	[Johnson (1991)]
	• Gag CTL response was studied in three individuals				
p17(19–27)	p17(19–27 JRCSF)	IRLRPGGKK	HIV-1 infection	scid-hu mouse(B*2705)	[Brander & Goulder(2001)]
	• Noted by Brander to be B*2705 (Pers. Comm. D. Lewinsohn)				
p17(19–27)	p17(19–27 LAI)	IRLRPGGKK		human(B27)	[Brander & Walker(1996)]
p17(19–27)	p17(19–27 JRCSF)	IRLRPGGKK	HIV-1 infection	scid-hu mouse(B27)	[McKinney (1999)]
	• Epitope-specific CTL were infused in infected human PBL-SCID mice, and transient decreases in viral load were observed, however virus was not eradicated and the HIV-specific CTL rapidly disappeared • No escape mutants were observed • Control CTL were long lived in both infected and uninfected mice, showing the rapid loss of CTL was due to target interaction				
p17(19–27)	p17( )	IRLRPGGKK	HIV-1 infection	human(B27)	[Goulder (2000a)]
	• WEKIRLRPGGKKKYKLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – 2/3 individuals that were B27+ had a dominant response to this epitope • Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses • Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa				
p17(19–27)	p17(19–27)	IRLRPGGKK	HIV-1 infection	human(B27)	[Day (2001)]
p17(19–27)	p17(19–27)	IRLRPGGKK	HIV-1 infection	human(B27)	[Goulder (2001c)]
	• Epitope name: IK9. This B27 epitope is generally recognized only if there is escape in the B27 dominant epitope, p24 KRWIILGLNK				
p17(20–28)	p17(20–28)	RLRPGGKKK	HIV-1 infection	human( )	[Betts (2000)]
	• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant • Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes • Three of the four individuals that responded to SLYNTVATL recognized HIV epitopes, and one individual who was A*0201, A31 and B51 and B58w4 recognized this epitope (previously described as HLA A3.1), as well as one other				

p17(20–28)	p17(20–28)	RLRPGGKKK	HIV-1 infection	human(A*03)	[Goulder (1997e), Goulder (1997a)]

- Identical twin hemophiliac brothers were both infected with the same batch of factor VIII
- One had a response to gag A3 epitope RLRPGGKKK, the other non-responder carried the sequence RLRPGGKKC
- [Goulder (1997a)] is a review of immune escape that summarizes this study

p17(20–28)	p17(20–28)	RLRPGGKKK	HIV-1 infection	human(A*0301)	[Brander & Goulder(2001)]

- C. Brander notes that this is an A*0301

p17(20–28)	p17( )	RLRPGGKKK	HIV-1 infection	human(A*0301)	[Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
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- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

p17(20–28)	p17(20–28 SF2)	RLRPGGKKK	HIV-1 infection	human(A*0301)	[Altfeld (2001a)]

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from seven proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study
- The reactive peptide p17 gag WEKIRLRPGGKKKYK contained two A*0301-restricted epitopes, KIRLRPGGK and RLRPGGKKK A*0301

p17(20–28)	p17(20–28)	RLRPGGKKK	HIV-1 infection	human(A3)	[Goulder (2000c)]

- Two clonal CTL responses were generated in donor 021-BMC (HLA A3/3001, B42/-, Cw17/-) against different optimal versions of this epitope, one nine amino acids long, one ten
- A previously described optimal A3 epitope overlapping this region, KIRLRPGGK, was not recognized by CTL from 021-BMC

p17(20–28)	p17(20–28)	RLRPGGKKK	HIV-1 infection	human(A3)	[Goulder (1997f)]

- A control CTL line that reacts with this peptide was included in the study

p17(20–28)	p17(20–28)	RLRPGGKKK	HIV-1 infection	human(A3)	[Cao (1997)]

- The consensus peptide of A, B, and D clade viruses is RLRPGGKKK
- The consensus peptide of C clade viruses is RLRPGGKKH and is equally reactive

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p17(20–28)	p17( )	RLRPGGKKK	HIV-1 infection	human(A3)	[Goulder (2000a)]

- WEKIRLRPGGKKKYKLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – 7/10 that had a dominant response to this epitope were A3, and 5/7 targeted RLRPGGKKK while 2/7 targeted KIRLRPGGK (this tally comes from the tables, not the text of the paper which stated 6/7 RLRPGGKKK)
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- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 5/7 group 1, 2/4 group 2, and 2/2 group 3

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p17(20–28)	p17(20–28)	RLRPGGKKK	HIV-1 infection	human(A3)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant

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p17(20–28)	p17(20–28)	RLRPGGKKK	HIV-1 infection	human(A3)	[Goulder (2001c)]

- Epitope name: RK9. Responses to this dominant A3-restricted Gag epitope are present during the time of decreasing viral load in acute infection
- Mutations in this epitope were observed in autologous clones of subjects who were A3-positive with a higher frequency than those who were A3-negative (P = 0.0002)
- These mutations are being sexually transmitted in adult infections

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p17(20–29)	p17(20–29 LAI)	RLRPGGKKKY	HIV-1 infection	human(A*0301)	[Brander & Goulder(2001)]
	• C. Brander notes this is an A*0301 epitope				
p17(20–29)	p17(20–29)	RLRPGGKKKY	HIV-1 infection	human(A3)	[Goulder (2000c)]
	• Two clonal CTL responses were generated in donor 021-BMC (HLA A3/3001, B42/-, Cw17/-) against different optimal versions of this epitope, one nine amino acids long, one ten • A previously described optimal A3 epitope overlapping this region, KIRLRPGGK, was not recognized by CTL from 021-BMC				
p17(20–29)	p17(20–29)	RLRPGGKKKY	HIV-1 infection	human(A3.1)	[Brander & Walker(1995)]
	• Unpublished, C. Jassoy and Beatrice Culman, pers. comm.				
p17(20–29)	p17(20–29 LAI)	RLRPGGKKKY	HIV-1 infection	human(A3.1)	[Wilkens & Ruhl(1999)]
	• Pers. comm., B. Wilkens and D. Ruhl				
p17(20–29)	p17(20–29)	RLRPGGKKKY	HIV-1 infection	human(A30, A3.1)	[Betts (2000)]
	• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant • Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes • 1/11 of the A2+ individuals was A30, and one was A3, and both responded to RLRPGGKKKY • The A2+ A3 individual also reacted with two other A3.1 epitopes				
p17(20–29)	p17(20–29 IIIB)	RLRPGGKKKY	HIV-1 infection	human(B42)	[Wilson (1996)]
	• Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study • RLRPGGKKRY, a naturally occurring variant, was found in non-transmitting mother and is recognized • Binds HLA-A3 and Bw62 as well				
p17(20–29)	p17(20–29)	RLRPGGKKKY	HIV-1 infection	human(B42, Bw62)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
p17(20–29)	p17(20–29)	RLRPGGKKKY	HIV-1 infection	human(B62)	[Brodie (2000)]
	• Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL • Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, co-localizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication • The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1α and MIP-1β, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism • This study provides a methodology for tracking and studying antigen specific CTL *in vivo*				
p17(20–29)	p17(20–29 LAI)	RLRPGGKKKY		human(Bw62)	[McMichael & Walker(1994)]
	• Review of HIV CTL epitopes • Also P. Johnson, pers. comm.				

p17(20–30)	p17( )	RLRPGGKKKYK	HIV-1 infection	human( )	[Goulder (2000a)]

- WEKIRLRPGGKKKYKLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – the dominant response in a Haitian immigrant living in Boston who was HLA A24/29 B7/B44 Cw6/7 was to this epitope, although the restricting element was not determined
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

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p17(20–35)	p17(90–105 SF2)	CLRPGGKKKYKLKHIV	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA A-2, A-24, B-13, B-35

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p17(21–35)	Gag( )	LRPGGKKKYKLKHIV	HIV-1 infection	human( )	[Weekes (1999a)]

- Peptide 703.3: Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28- CD8+ CTLp populations

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p17(21–35)	p17(91–105 SF2)	LRPGGKKKYKLKHIV	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA-A1, A2, B50, B57

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p17(21–35)	Gag( )	LRPGGKKKYKLKHIV	HIV-1 infection	human(A3)	[Weekes (1999b)]

- Peptide 703.3: Almost all CD8+ T-cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed in the CD28 depleted cell population
- HIV CTL responses to 3 Env and 2 Gag peptides were studied
- The clonal composition of TCR Vβ responses was studied and was found to be highly focused, with one TCR β-chain sequence tending to dominate the peptide-specific response – clones to this epitope were Vβ13.1 and Vβ5.2

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p17(21–35)	p17(21–35)	LRPGGKKKYKLKHIV		human(B8)	[Nixon & McMichael(1991)]

- Two CTL epitopes defined (see also p24(191-205))

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p17(21–35)	p17(21–35)	LRPGGKKKYKLKHIV	HIV-1 infection	human(not B8)	[van Baalen (1996)]

- Unknown HLA specificity, but not B8

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p17(21–40)	p17(21–40 clade A)	LRPGGKKKYRLKHLV-WASRE	HIV-1 infection	human(Cw4)	[Dorrell (1999)]

- CTL responses in three individuals with non-clade B infections were studied, two with subtype A infections, one with subtype C – their infections all originated in East Africa
- This epitope was defined in an A subtype infection – the B clade variant (LRPGGKKKYKLKHIVWASRE) has two mutations relative to the A subtype form, and the CTL from this patient were not A-B cross-reactive

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p17(22–31)	Gag(22–31)	RPGGKKRYKL	HIV-1 infection	human(B7)	[Jin (2000b)]

- This B7 epitope is one of three subdominant CTL responses detected in a long-term non-progressor
- A dominant B7 epitope was defined using conventional methods, and three additional sub-dominant HLA B7 epitopes were defined by first using a non-anchor based strategy, EpiMatrix, to identify 2078 possible epitopes in the autologous HIV-1, followed by B7 anchor residue prediction to narrow the set to 55 peptides for experimental testing

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p17(24–31)	p17(24–31)	GGKKKYKL		human(B8)	[Goulder (1997g)]

- The crystal structure of this peptide bound to HLA-B8 was used to predict new epitopes and the consequences of epitope variation
- The predictions were experimentally confirmed
- The anchors for HLA-B8 epitopes, as defined by peptide elution data, are P3 (K), P5 (K/R), and P8 (L)
- Structural data suggests that a positive charge at P5 is essential, but that the constraints on P3 may be less severe
- Small hydrophobic residues at P2 may be favorable for binding
- A spacious F-pocket favors mid-sized hydrophobic residues in the C-term anchor

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p17(24–31)	p17(24–31 SF2)	GGKKKYKL	HIV-1 infection	human(B8)	[McAdam (1998)]

- CTL from a patient infected with clade B virus did not recognize Ugandan variants of this epitope

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p17(24–31)	p17(24–31 LAI)	GGKKKYKL	HIV-1 infection	human(B8)	[Reid (1996)]

- The variants 7R: GGKKKYRL, 7Q: GGKKKYQL, 5R: GGKKRYKL, and 3R: GGRKKYKL, were studied
- Crystal structures were obtained to study these peptides in the context of HLA-B8, and CTL binding and activity were determined
- 3R has been detected in 3 patients, and it abolishes recognition causing extensive conformational changes upon binding including MHC main chain movement
- 7Q and 7R alter the TCR exposed surface, and retain some recognition
- Reactivity of 5R depends on the T-cell clone, this amino acid is embedded in the C pocket of B8 when the peptide is bound
- Optimal peptide is 8-mer, not 9-mer, and positions 3, 5, and 8 are the anchor residues

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p17(24–31)	p17(24–31 LAI)	GGKKKYKL	HIV-1 infection	human(B8)	[Price (1997)]

- A weak CTL response to the index peptide was observed in an HLA-B8+ infected individual
- Sequences from the earliest available time point showed that a variant at position 5, an anchor residue, GGKKQYKL, was present

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p17(24–31)	p17(24–31 SF2)	GGKKKYKL	HIV-1 infection	human(B8)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection

	• The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef • Previously described and newly-defined optimal epitopes were tested for CTL response • Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 1/3 group 2, and 2/2 group 3				
p17(24–31)	p17(24–31)	GGKKKYRL	HIV-1 exposed seronegative, HIV-1 infection	human(B8)	[Kaul (2001a)]
	• ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers				
p17(24–31)	p17(24–31)	GGKKKYKL	HIV-1 infection	human(B8)	[Day (2001)]
	• B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual				
p17(24–32)	p17(24–32 LAI)	GGKKKYKLK	HIV-1 infection	human(B*0801)	[Brander & Goulder(2001)]
	• C. Brander notes epitope to be presented by B*0801				
p17(24–32)	p17(24–32 LAI)	GGKKKYKLK	HIV-1 infection	human(B8)	[Sutton (1993)]
	• Exploration of HLA-B8 binding motif through peptide elution				
p17(24–32)	p17(24–32 LAI)	GGKKKYKLK	HIV-1 infection	human(B8)	[Rowland-Jones (1993)]
	• Study of an individual with partially defective antigen processing				
p17(24–32)	p17(24–32)	GGKKKYKLK	HIV-1 infection	human(B8)	[Klenerman (1994)]
	• Naturally-occurring variants GGKKKYQLK and GGKKRYRLK may act as antagonists				
p17(24–32)	p17(24–32)	GGKKKYKLK	HIV-1 infection	human(B8)	[Klenerman (1995)]
	• Naturally-occurring antagonist GGKKKYQLK found in viral PBMC DNA and RNA				
p17(24–32)	p17(24–32)	GGKKKYKLK	HIV-1 infection	human(B8)	[Nowak (1995)]
	• Longitudinal study of CTL response and immune escape – the variant GGRKKYKLK binds to HLA-B8 but is not reactive				
p17(24–32)	p17(24–32)	GGKKKYKLK	HIV-1 infection	human(B8)	[Dyer (1999)]
	• CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective • Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load				
p17(24–32)	p17( )	GGKKKYKLK		human(B8)	[Rowland-Jones (1999)]
	• CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5				

- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective
- HIV-2 sequence: GGKKKYKMK – no cross-reactivity [Phillips (1991)]

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p17(24–33) p17(24–32) GGKKKKYKLK HIV-1 infection human(B8) [Oxenius (2000)]

- Epitope name: GGK. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- This epitope was recognized by 1/7 study subjects that were HLA-B8+
- Patient SC12(HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKKKYKLK – GEIYKRWII and GGKKKYKLK responses were stimulated by a brief period off therapy

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p17(24–33) p17( ) GGKKKKYKKL HIV-1 infection human(B8) [Seth (2001)]

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized

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p17(24–35) p17(25–35 SF2) GGKKKYKLKHIV HIV-1 infection human(B8) [Goulder (1997a), Phillips (1991)]

- Longitudinal study of CTL escape mutants in people with the appropriate HLA types – little variation was observed in the immunodominant B27 epitope, relative to B8 epitopes, which varied over time
- [Goulder (1997a)] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA B27 patients

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p17(24–35) p17(25–35) GGKKKYKLKHIV HIV-1 infection human(B8) [Birk (1998)]

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs

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p17(28–36) ( ) KYRLKHLVW HIV-1 infection human( ) [Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized in 1/22 HEPS sex worker controls (ML1573)

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p17(28–36) p17(28–36 LAI) KYKLKHIVW human(A*2402) [Brander & Goulder(2001)]

- Ikeda-Moore(1998) and D. Lewinsohn, pers. comm.
- C. Brander notes that this is an A*2402 epitope

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p17(28–36)	p17(28–36 SF2)	KYKLKHIVW	HIV-1 infection	human(A*2402)	[Ikeda-Moore (1998)]

- Strong CTL activity to this peptide was detected in 2/3 HIV-infected individuals who were HLA A24+
- HLA A24 is very common in Japanese (70% carry it) and is common globally
- This epitope was detected by looking for peptides with appropriate A24 anchor residues (Y at position 2, carb-term ILF or W) – 16/17 such peptides bound to A24 – KYKLKHIVW was found to be a naturally processed epitope that elicits a strong CTL response.

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p17(28–36)	p17(28–36 LAI)	KYKLKHIVW		human(A23)	[Goulder & Walker(1999)]

- P. Goulder, pers. comm.

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p17(28–36)	p17(28–36 LAI)	KYKLKHIVW		human(A24)	[Brander & Walker(1996)]

- D. Lewinsohn, pers. comm.

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p17(28–36)	p17(28–36 SF2)	KYKLKHIVW	HIV-1 infection	human(A24)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A24+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 2/3 group 2, and 0/0 group 3

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p17(28–36)	p17(28–36 93TH253 CRF01)	KYKLKHIVW	HIV-1 infection	human(A24)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested
- The only HLA-A24 FSWs tested did not recognized the E clade version of this epitope KYKMKHLVW, which differs from the previously defined B clade version by two amino acids, KYKLKHIVW
- This epitope was only conserved in CRF01 (subtype E), and identities were rare

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p17(28–36)	p17(728–736 subtype A)	KYRLKHLVW	HIV-1 exposed seronegative, HIV-1 infection	human(Cw4)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure

- Among HLA-Cw4 women, 2/2 HEPS and 7/11 HIV-1-infected women recognized this epitope
- The dominant response to this HLA allele was to this epitope in both of the 2/2 HEPS cases and in 3 of the 7/11 HIV-1-infected women

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p17(28–36) p17(28–36) KYRLKHLVW HIV-1 infection human(Cw4) [Appay (2000)]

- This epitope is newly-defined in this study
- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV
- HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

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p17(36–44) p17( ) WASRELERF HIV-1 infection human( ) [Goulder (2000a)]

- The dominant response in an African American who was HLA A3/33 B35/B53 Cw4/7 was to this epitope, although the restricting element was not determined – this epitope fell outside the most recognized peptides in the study
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

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p17(36–44) p17(35–43 LAI) WASRELERF HIV-1 infection human(B*3501) [Goulder (1997d)]

- Optimal epitope defined from within p17(30-44), LKHIVWASRELERFA
- Dominant CTL response in an HIV+ asymptomatic donor was to this epitope
- The Phe in the C-term anchor is distinct from the previously-defined Tyr for B*3501 C-term anchors

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p17(36–44) p17(36–44 LAI) WASRELERF human(B*3501) [Brander & Goulder(2001), Goulder (1997b)]

- C. Brander notes this is a B*3501 epitope

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p17(36–44) p17(36–44) WASRELERF HIV-1 infection human(B35) [Birk (1998)]

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs

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p17(36–44) p17(36–44) WASRELERF HIV-1 infection human(B35) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p17(36–44)	p17(36–44 SF2)	WASRELERF	HIV-1 infection	human(B35)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 0/2 group 2, and 1/1 group 3

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p17(69–93)	p17(69–93 BH10)	QTGSEELRSLYNTVAT-LYCVHQRIE	HIV-1 infection	human(A2)	[Johnson (1991)]

- Gag CTL response studied in three individuals

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p17(71–79)	p17(71–79 LAI)	GSEELRSLY		human(A1)	[Brander & Walker(1996)]

- P. Goulder, pers. comm.

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p17(71–79)	p17(71–79)	GSEELRSLY	HIV-1 infection	human(A1)	[Birk (1998)]

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs

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p17(71–79)	p17(71–79 HXB2)	GSEELRSLY	HIV-1 infection	human(A1)	[Oxenius (2000)]

- Epitope name: GSE. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- This epitope was not recognized by the 6/8 study subjects that were HLA-A1

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p17(71–79)	p17(71–79)	GSEELRSLY	HIV-1 exposed seronegative, HIV-1 infection	human(A1)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-A1 women, 1/1 HEPS and 3/3 HIV-1-infected women recognized this epitope, and the response was the dominant HLA-A1 response in all cases

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p17(71–85)	p17(71–85 SF2)	GSEELRSLYNTVATL	HIV-1 infection	human( )	[Lieberman (1997a)]
	• Of 25 patients, most had CTL specific for more than one HIV-1 protein • Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag • One of these 12 had CTL response to this peptide • The responding subject was HLA-A1, A11, B8, B27				
p17(74–82)	p17( )	ELRSLYNTV		human(B*0801)	[Brander & Goulder(2001)]
	• Noted by Brander to be a B*0801 epitope				
p17(74–82)	p17( )	ELRSLYNTV		human(B8)	[Goulder (1997g)]
	• Defined in a study of the B8 binding motif				
p17(74–82)	p17(74–82)	ELRSLYNTV	HIV-1 infection	human(B8)	[Birk (1998)]
	• A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs				
p17(74–82)	p17(74–82)	ELRSLYNTV	HIV-1 infection	human(B8)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
p17(74–82)	p17(74–82)	ELRSLYNTV	HIV-1 infection	human(B8)	[Day (2001)]
	• B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual				
p17(76–86)	p17(74–86 LAI)	RSLYNTVATLY		human(A*3002)	[Brander & Goulder(2001)]
	• C. Brander notes this is an A*3002 epitope				
p17(76–86)	p17( )	RSLYNTVATLY	HIV-1 infection	human(A*3002)	[Goulder (2000a)]
	• The CTL-dominant response was focused on this epitope in a single HIV+ individual from Boston – this epitope fell outside the most recognized peptides in the study • Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses • Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa				
p17(76–86)	Gag(76–86 HXB2)	RSLTNTVATLY	HIV-1 infection	human(A*3002)	[Mulligan (2001)]
	• Epitope G8 from Patient 07107 with HLA genotypes A*3002, A*3201, B*4501, B*5301, Cw*0401, Cw*1202				

p17(76–86)	Gag( )	RLSYNTVATLY		human(A*3002)	[Novitsky (2001)]

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort
- Only 3/13 (23.1%) A*3002-positive subjects demonstrated moderate CTL responses to the peptide GTEELRSLYNTVATLYCVHE (residues 71 to 90), which contains the previously described A*3002 epitope RLSYNTVATLY

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p17(76–86)	p17(76–86)	RSLYNTVATLY	HIV-1 infection	human(A*3002)	[Goulder (2001a)]

- Epitope name: RY11 (p17). HLA-A*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule
- A rapid method was developed combining ELISPOT with intracellular IFN-γ staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood
- Two individuals were studied: Subject 199 (HLA A*0201/*3002 B*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A*3002/ B53/*5801 Cw4/7) an African-Caribbean
- In both HLA-A*3002 individuals the response to RSLYNTVATLY was dominant
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)
- HLA-A*3001-positive targets do not present RSLYNTVATLY

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p17(76–86)	p17(74–86 SF2)	RSLYNTVATLY	HIV-1 infection	human(A30)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A30+ individuals that had a CTL response to this epitope broken down by group: 0/1 group 1, 0/0 group 2, and 1/1 group 3

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p17(77–85)	p17( )	SLYNTVATL	HIV-1 infection	human( )	[Sewell (2000)]

- Review of the impact of CTL on viral immunity and escape that notes that SLYNTVATL-tetramer binding cells in individuals that react to this epitope inversely correlate with plasma viral load

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A*02)	[Huang (2000)]

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed
- Increases in γ IFN producing cells were observed in response to anti-retroviral therapy using single cell IFN-γ-production ELISPOT
- 4/8 A*02 subjects had a positive response to this epitope indicating that it is a major epitope for CD8+ γ IFN production
- In 3/3 HLA A*02, B*27 individuals, the dominant response in gag measured by both γ IFN production and T-cell lysis was a B27 epitope, p24(263-272), not the A2 SLYNTVATL epitope

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A*02)	[Rinaldo (2000)]

- Epitope name: SL9. Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that can persist after therapy and long periods of virus being below the level of detection

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p17(77–85) p17( ) SLYNTVATL HIV-1 infection human(A*02) [Scott-Algara (2001)]

- Epitope name: SL9. This study examined with CTL response in HLA A*02+ children by tetramer staining for HLA-A2 immunodominant epitopes SLYNTVATL and ILKEPVHGV
- 71% of the 28 HIV-1 infected HLA-A*02 positive children recognized both epitopes, with cells from 26 children stained positive by the gag tetramer (SLYNTVATL) and 21 children by the pol tetramer (ILKEPVHGV)
- There were no differences observed in children that had therapy versus those that did not
- Tetramer-binding cells were memory activated CD28-, CD45RO+, CD45RA- HLADR+, CD69-, CD8+ T-cells

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p17(77–85) p17(77–85 HXB2) SLYNTVATL HIV-1 infection human(A*0201) [Brander (1999)]

- Epitope name: SL9. Multiple natural variations in the SL9 flanking regions of the immunodominant epitope SLYNTVATL were tested and found not to adversely affect CTL recognition or prevent epitope processing, suggesting that viral escape from the HLA-A*0201-restricted CTL response against SLYNTVATL is probably not linked to variations in the flanking regions of this epitope
- The substitution Y79F was an escape mutation in that it interfered with CTL recognition by one CTL clone from an A*0201 infected individual, clone 13010.B17, but it was still recognized by another CTL clone, 115.D4

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p17(77–85) Gag( ) SLYNTVATL HIV-1 infection human(A*0201) [Tan (1999)]

- Adoptive transfer of two autologous *in vitro*-expanded CTL clones against the A*0201 restricted epitopes SLYNTVATL and VIYQYMDDL were infused into a patient – they were well tolerated, but the SLYNTVATL clone was shown by tetramer staining to be rapidly eliminated through apoptosis, and the treatment had no impact upon viral load and CD4 and CD8 cell counts

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p17(77–85) p17(77–85) SLYNTVATL HIV-1 infection human(A*0201) [Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninty five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- Individuals that did not respond to SLYNTVATL recognized other HIV epitopes, and 2/4 SLYNTVATL responders had stronger responses to epitopes restricted by other class I alleles
- SLYNTVATL was the only response detected in a one individual that was HLA A*0201, B44, B70

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p17(77–85) p17(77–85) SLYNTVATL HIV-1 infection human(A*0201) [Ogg (1999)]

- Epitope name: SL9. CTL effector levels were measured after potent ARV therapy using HLA-tetramer complexes for the A*0201 epitopes SLYNTVATL and ILKEPVHGV in seven patients, and the B*3501 epitope DPNPQEVVL in one additional patient
- Levels of CTL effectors typically decline for 5-7 days and then rebound, fluctuating during the first two weeks of therapy
- After the early fluctuation, there was a steady exponential decay with a median half-life of 45 days

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p17(77–85) p17(77–85) SLYNTVATL HIV-1 infection human(A*0201) [Altman (1996)]

- Epitope name: SL9. This paper introduces the tetramer methodology which permits quantification of specific CTL based on expression of specific TCRs – HLA-A2 tetramers were prepared that can stain CTL lines specific for ILKEPVHGV and SLYNTVATL, and can quantitate HIV-specific CD8+ cell lines in freshly isolated PBMCs

		• Three patients only stained the Gag epitope SLYNTVATL, one patient had the highest frequency of tetramer staining to the Pol epitope (0.77%), less to the Gag epitope (0.28%)			
p17(77–85)	Gag( )	SLYNTVATL	HIV-1 infection	human(A*0201)	[Gray (1999)]
	• Administration of highly active antiretroviral therapy (HAART) reduced CD8+ cell frequency, and the CD8+ cells detected by tetramer staining were likely to be memory cells, indicating that persistently replicating viral populations are needed to maintain high frequencies of HIV-1 specific CTL				
p17(77–85)	p17(77–85 SF2)	SLYNTVATL	HIV-1 infection	human(A*0201)	[McAdam (1998)]
	• Epitope name: SL9. CTL from a patient infected with clade B virus did not recognize the clade A analog of this epitope				
p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A*0201)	[Wilson (1998a)]
	• Epitope name: SL9. HIV+ individuals were followed longitudinally using MHC tetramers in combination with 14 anti-BV chain MAbs, and clonal expansion of HIV-specific T-cells was followed *in vivo* • Seven HIV+ people were studied, and all showed expansions of particular TCR BV clones, often several, relative to uninfected controls • Three patients were followed in detail, TCR VB expansions persisted for 2 to 3 years, with occasional transient increases • An A2-Gag specific line from one patient was found to be BV8, and at its highest level represented 17.5% of the patient's CD8+ T-cells				
p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A*0201)	[Ogg (1998b)]
	• Epitope name: SL9. HLA-tetrameric complexes were used in a cross-sectional study of 14 untreated HLA A*0201 positive individuals, revealing an inverse relationship between HIV Gag and Pol specific CTL effector cells (CTLe) and viral load • Inclusion of both the p17 SLYNTVATL and RT ILKEPVHGV epitopes gives a good representation of HLA A*0201-restricted activity • No correlation was observed between the CTLe and CD4 count or clearance rate of productively infected cells				
p17(77–85)	p17(77–85)	SLYNTVATL	*in vitro* stimulation	human(A*0201)	[Walter (1997)]
	• Epitope name: SL9. HLA-A2 heavy chain and β2-microglobulin expressed in *E. coli* were refolded in the presence of this peptide • The HLA-A2-peptide complex elicited HLA-A2 peptide-specific CTL response in cells lacking HLA-A2 • Suggests that preformed HLA-peptide complexes could provide an alternate to intracellular processing for immunogens				
p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A*0201)	[Lalvani (1997)]
	• Epitope name: SL9. A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers • This peptide was one of the test peptides for optimizing the protocol				
p17(77–85)	p17(76–84)	SLYNTVATL	*in vitro* stimulation	human(A*0201)	[van der Burg (1996)]
	• Epitope name: SL9. Slow dissociation rate is associated with immunogenicity • CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual				

p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A*0201)	[Goulder (1997e), Goulder (1997a)]

- Epitope name: SL9. Identical twin hemophiliac brothers were both infected with the same batch of factor VIII
- One had a response to gag A2 epitope SLYNTVATL, the other to pol A2 epitope ILKEPVHGV
- Viral sequencing from the twin that had no response to SLYNTVATL indicated his virus had the substituted form SLHNAVAVL
- 71% of an additional set of 22 HIV-1 infected HLA-A*0201 positive donors preferentially responded to gag SLYNTVATL
- Those individuals with a pol ILKEPVHGV response tended to have mutations in or around SLYNTVATL
- An additional subject went from SLYNTVATL responder to non-responder coincident with a switch to the variant SLFNTVATL
- [Goulder (1997a)] is a review of immune escape that summarizes this study

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p17(77–85)	Gag(77–85)	SLYNTVATL	HIV-1 infection	human(A*0201)	[Gray (1999)]

- Epitope name: SL9. Peptide-tetramer complexes of A*0201 and SLYNTVATL or ILKEPVHGV were used to study individuals receiving HAART to determine the frequency of Class I HLA-restricted anti-HIV CD8+ T-cells
- 17/18 asymptomatic patients had a CTL response to one or both epitopes – 72% had a CTL response to SLYNTVATL
- After HAART, the majority of the epitope-specific CTL were apparently memory cells

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p17(77–85)	p17(77–85 clade A)	SLFNTVATL	HIV-1 infection	human(A*0201)	[Dorrell (1999)]

- Epitope name: SL9. CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa
- This epitope is most commonly SLYNTVATL in B subtype, and CTL from the C subtype infection did not recognize B clade gag or the 3Y form of the epitope, but do recognize the predominant A and C clade form, SLFNTVATL

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A*0201)	[Brander (1998)]

- Epitope name: SL9. Of 17 infected HLA A*0201 subjects, 13 had CTL responses against the p17 SLYNTVATL epitope, six recognized ILKEPVHGV and five recognized VIYQYMDDL, and there was no correlation between viral load and recognition of a specific epitope
- Only one subject had CTL against all three epitopes
- There was significant heterogeneity in the CTL response to this immunodominant epitope
- The overall variation in this epitope among the 17 who had a CTL response and 11 non-HLA A*0201 HIV-1+ individuals was similar, suggesting a lack of immune pressure
- Subjects were part of the San Francisco City Clinic Cohort, the ARIEL project and from the Boston area

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p17(77–85) p17(77–85 HXB2) SLYNTVATL HIV-1 infection human(A*0201) [Hay (1999)]

- Epitope name: SL9. CTL response to IPRRIRQGL was the immunodominant response in a rapid progressor – there was a subdominant response to SPAIFQSSM in Pol, and interestingly, no response to commonly immunodominant HLA A*0201 epitope SLYNTVATL, although this individual was HLA A*0201
- The individual showed a strong initial CTL response at the time of the initial drop in viremia, but it was quickly lost, although memory cells persisted
- Despite the initial narrow response to two epitopes, no other CTL responses developed
- No HIV-specific lymphoproliferative responses were detected in this patient, and neutralizing antibody response was weak
- A variant of this epitope was observed *in vivo* (`--F----V-`), but this mutation is recognized by SLYNTVATL-specific CTL, and in this case the patient's cells could present the peptide to SLYNTVATL-specific CTL

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p17(77–85) p17(77–85) SLYNTVATL HIV-1 infection human(A*0201) [Kalams (1999b)]

- Two patients were followed before and after HAART – reduced plasma HIV-1 RNA levels resulted in a decline in HIV-specific *in vivo*-activated CTL such that by day 260 CTL activities were undetectable
- ERYLKDQQL was the dominant response in one of the individuals, SLYNTVATL subdominant
- Sporadic breakthrough in viremia resulted in transient increases in CTLp
- Memory CTL frequency directed against Vac-Gag, Vac-RT, Vac-Env, and Vac-Nef initially increased with HAART and then decreased with the decline of the viral load

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p17(77–85) Gag(77–85) SLYNTVATL HIV-1 infection human(A*0201) [Spiegel (2000)]

- High levels of CD8+ HIV-1 specific and cytomegalovirus specific CTL were detected by HLA-A*0201-peptide tetramers in 3 infected subjects with very low CD4 counts, but CD8 T-cell mediated effector activity was not seen
- Thus HIV-1 specific CD8+ cells may be present but may lack direct effector activity in late disease, suggesting that overcoming antigen unresponsiveness may be a useful therapeutic strategy

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p17(77–85) Gag(77–85) SLYNTVATL HIV-1 infection human(A*0201) [Larsson (1999)]

- ELISPOT was used to assay the CD8 T-cell response to the HIV-1 proteins Gag, Pol, Nef or Env expressed in vaccinia vectors in 19 HIV+ people
- The highest CTL frequency was directed at Pol epitopes
- In A*0201 individuals, higher numbers of spot-forming T-cells were directed against HIV-1 proteins expressed in vaccinia than to peptides SLYNTVATL and ILKEPVHGV presented by A2

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p17(77–85) p17( ) SLYNTVATL HIV-1 infection human(A*0201) [Goulder (2000a)]

- The CTL-dominant response was focused on this epitope in 11/25 HLA A2 (A*0201 or A*0202) HIV+ individuals from Boston and in 1/8 HLA A2 HIV+ individuals from Durban
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses

- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

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p17(77–85) p17(77–85 LAI) SLYNTVATL human(A*0201) [Brander & Goulder(2001)]

- C. Brander notes this is an A*0201 epitope

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p17(77–85) p17(77–85 SF2) SLYNTVATL HIV-1 infection human(A*0201) [Goulder (2001b)]

- Epitope name: SL9. This epitope is targeted by 75% of HLA-A*0201, HIV+ adults, and the magnitude of the response is inversely correlated with viral load
- CTL responses to SL9 and autologous SL9 variants were not detected in 11 HLA-A*0201 positive subjects during acute infection
- Longitudinal studies of two individuals (AC13 and PI004) showed that the initial control of viremia was independent of the SL9 CTL response
- Low Gag expression levels did not correlate with the delayed CTL response to this epitope
- Autologous SL9 variants SLYNTIAVL, SLYNTVAVL, SLFNTVATL, SLFNTVATL, and SLFNTVATL are each capable of inducing a range of CTL responses, sometimes strong, sometimes diminished, and sometimes complete escape relative to the wild type variant SLYNTVATL in patients with chronic HIV-1 infection – the ability to cross-react with a particular variant was patient dependent

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p17(77–85) p17( ) SLYNTVATL HIV-1 infection human(A*0201) [Altfeld (2001d)]

- Epitope name: p17 SL9. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, including p17 SL9, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- p17 SL9 was recognized in 12/22 patients with chronic HIV-1 infection
- Only 1/13 patients with acute HIV-1 infection recognized p17 SL9

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p17(77–85) Gag( ) SLYNTVATL HIV-1 infection human(A*0201) [Goepfert (2000)]

- Epitope name: (SL9). This paper describes a comparison of results of different CTL assays, an SL9 tetramer assay and IFN-γ ELISPOT, using 7 HIV-positive patients
- The IFN-γ ELISPOT assay was compared using the single SL9, a pool of overlapping 20 mers, and recombinant vaccinia encoding Gag as antigen – pooled peptides gave the highest number of spot forming cells, vaccinia gave high background
- A correlation with results of the tetramer assay was found only for ELISPOT using the Gag epitope as antigen, but the tetramer assay detected a 10-fold higher number of cells than could produce IFN-γ in the ELISPOT assay – the authors suggest not all tetramer-positive cells may produce IFN-γ, some may be undergoing apoptosis, some may be producing other cytokines
- The tetramer assay could detect a reaction to SLYNTVATL in most of the HLA-A*0201 chronically HIV-1 infected study subjects

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p17(77–85)	Gag( )	SLYNTVATL	*in vitro* stimulation	human(A*0201)	[Engelmayer (2001)]

- Recombinant canarypox virus vector containing HIV-1 sequences, upon infection of mature dendritic cells, can trigger specific lysis through *in vitro* by T-cells from HIV-1 infected individuals at levels comparable to the response seen to HIV carried in vaccinia vectors
- Recombinant canarypox virus vector containing HIV-1 sequences can also stimulate HIV-specific CD4+ helper T-cell responses

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p17(77–85)	p17(77–85 LAI)	SLYNTVATL	HIV-1 infection	human(A*0201)	[Mollet (2000)]

- Epitope name: G3. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using tetramer staining or CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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p17(77–85)	Gag( )	SLYNTVATL	HIV-1 infection	human(A*0201)	[Gea-Banacloche (2000)]

- In a study including many long-term non-progressors, no correlation between plasma virus levels and number of HIV-specific CD8+ T-cells was found
- High frequencies of circulating CD8+ T-cells were HIV-1 specific, and the majority of these responses were to gag-pol gene products
- 4/21 subjects were HLA-(A*0201), and of these only 2 subjects (patient 3 and 19) tested positive to this epitope

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p17(77–85)	p17(77–85 SF2)	SLYNTVATL	HIV-1 infection	human(A*0201)	[Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- Tetramer staining with A2, β2-microglobulin, and either SLYNTVATL, KLVGKLNWA, or LTFGWCFKL revealed that tetramers detected more HIV-specific cells in LTNP than in progressors, activated effector cells were the minority population, and ELISPOT correlated better with the effector cell subpopulation than the total tetramer stained population

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p17(77–85)	Gag(77–85)	SLYNTVATL	HIV-1 infection	human(A*0201)	[Jin (2000a)]

- The CTL effector levels (CTLe) were compared in long term non-progressors (LTNP) with low viral load and in patients whose virus was well-suppressed by therapy, using a tetramer assay
- LTNPs have high memory CTLe numbers and low viral load, while HAART patients had low CTLe numbers and low viral load

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A*0201)	[Appay (2000)]

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV
- HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation

- In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

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p17(77–85) p17(77–85) SLYNTVATL HIV-1 infection human(A*0201) [Goulder (2000b)]

- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA])
- HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection

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p17(77–85) p17( ) SLYNTVATL HIV-1 infection human(A*0201) [Ostrowski (2000)]

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T-cell help in 9/10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T-cell help to a variable degree in most of patients
- Those CTL that didn't respond to CD40LT could expand with IL-2 present, and IL-15 produced by dendritic cells also contributes
- The T-helper epitope used for CD4+ T-cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKANSKFIGITE)

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p17(77–85) p17(77–85) SLYNTVATL human(A*0202) [Brander & Goulder(2001)]

- C. Brander notes that this epitope can be presented by A*0201 and A*0202

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p17(77–85) p17( ) SLYNTVATL HIV-1 infection human(A*0202) [Goulder (2000a)]

- The CTL-dominant response was focused on this epitope in 11/25 HLA A2 (A*0201 or A*0202) HIV+ individuals from Boston and in 1/8 HLA A2 HIV+ individuals from Durban
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

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p17(77–85) p17(77–85 LAI) SLYNTVATL human(A*0205) [Brander & Goulder(2001)]

- C. Brander notes that this epitope can be presented by A*0201 and A*0202

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p17(77–85) p17( ) SLYNTVATL HIV-1 exposed seronegative human(A*0214, A*0201) [Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells
- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women
- The epitope variants SLYNTVATL and SLFNTVATL were both recognized

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p17(77–85) Gag(77–85) SLYNTVATL Vaccine human(A2) [Woodberry (1999)]

Vaccine: *Vector/type:* vaccinia *HIV component:* polyepitope

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested
- SLYNTVATL was recognized by 5/16 HLA-A2 patients

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p17(77–85) p17(77–85) SLYNTVATL Vaccine human(A2) [Carruth (1999)]

Vaccine: *Vector/type:* canarypox *Strain:* MN, LAI *HIV component:* gp120, gp41, Gag, Protease

- The vaccine used was a live recombinant canarypox (CP) virus vaccine containing multiple HIV-1 genes (HIV-1 MN gp120, HIV-1 LAI gp41, HIV-1 LAI Gag, HIV-1 LAI protease)
- CD4+ and CD8+ Gag and Env specific CTL responses were detected in only 1/5 vaccinated volunteers, and were not detectable 1 year after vaccination
- CTL responses to epitopes SLYNTVATL and TVYYGVPVWK from HIV+ control patients were used as positive controls
- The study explored why vaccinees were non-responsive – non-response was not due to inherent defects or differences in the ability of these individuals to process and present antigen
- Lack of response to SLYNTVATL led the authors to speculate that the immunodominance of this epitope in natural infections may not be recapitulated by vaccine antigen

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p17(77–85) p17(77–85) SLYNTVATL HIV-1 infection human(A2) [Birk (1998)]

- Epitope name: SL9. A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs

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p17(77–85) p17(77–85) SLYNTVATL HIV-1 infection human(A2) [Callan (1998)]

- Epitope name: SL9. Included as a negative control in a tetramer study of A2-EBV CTL response

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p17(77–85) p17( ) SLYNTVATL HIV-1 infection human(A2) [Wagner (1998a)]

- Epitope name: SL9. CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1 α and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules

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p17(77–85)	p17(77–85 HXB2)	SLYNTVATL	HIV-1 infection	human(A2)	[Collins (1998)]

- Epitope name: SL9. Two CTL clones recognize this epitope, but not the NL4-3 form of the epitope SLYNTIAVL
- Nef down-regulates MHC class I molecules, which inhibits CTL killing, and this down-regulation can be partially compensated for by adding excess soluble peptide

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A2)	[Durali (1998)]

- Epitope name: SL9. Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env
- Patient B18 had the greatest breadth and diversity of response, and recognized Gag SLYNTVATL and Nef PLTFGWCFKL

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A2)	[Kundu (1998b)]

- Epitope name: SL9. Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated
- SLYNTVATL is a conserved HLA-A2 epitope included in this study – 3/6 patients had this sequence as their HIV direct sequence, one had the form SLYNTVAVL and all four of these had a detectable CTL response – the other two had either the sequence SLFSAVAVL or SLFSAVAAL and no detectable CTL response

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p17(77–85)	p17(77–85 IIIB)	SLYNTVATL	HIV-1 infection	human(A2)	[Sipsas (1997)]

- Epitope name: SL9. HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB
- SLYNTVAVL, a variant found in HIV-1 MANC, was also recognized
- SLFNTVAVL, a variant found in HIV-1 NY5CG, was also recognized

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p17(77–85)	p17( )	SLYNTVATL	HIV-1 infection	human(A2)	[Rowland-Jones (1998a)]

- Epitope name: SL9. A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating
- The A subtype consensus is SLfNtvatL
- The D subtype consensus is SLyNTvATL

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p17(77–85)	p17( )	SLYNTVATL	HIV-1 infection	human(A2)	[Sewell (1997)]

- Epitope name: SL9. Naturally-occurring variants of this epitope escaped killing and acted as antagonists

- The following variants were found in HIV-1 infected patients who mounted a strong response against this epitope: `--F------`, `--F----V-`, `--S------`, `-SF------`, `--L------`, `-----I---`, `-----I-V-`, `--F--I---`, `--F--I-V-`, `--F-A----`
- All variants bound to A2 with at least half the affinity of SLYNTVATL except the triple mutant: `--F--I-V-`
- Antagonism could be observed at low concentrations, abrogating lysis at an antagonist:agonist ratio of 1:10 – the antagonism was observed in one SLYNTVATL-specific CTL line but not another

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p17(77–85)	p17(77–85 HXB2)	SLYNTVATL	HIV-1 infection	human(A2)	[Yang (1997b)]

- Epitope name: SL9. A chimeric universal T-cell receptor was created by linking CD4 or an HIV-specific anti-gp41 Ig sequence to the signaling domain of the T-cell receptor chain ζ, and transduced into CD8+ cells
- The response using universal-receptor-bearing CD8+ cells to lyse infected cells *in vitro* was comparable to the natural occurring responses of CTL-clones from HIV+ individuals in terms of kinetics and efficiency
- A CTL clone specific for this epitope was used for the comparison

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p17(77–85)	p17(77–85)	SLYNTVATL	*in vitro* stimulation	human(A2)	[Stuhler & Schlossman(1997)]

- Epitope name: SL9. Keyhole limpit hemocyanin or tetanus toxoid Th epitope co-expression with peptide CTL epitopes on the same APC was required for induction of peptide-specific CTL

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A2)	[Yang (1996)]

- Epitope name: SL9. CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones
- The distinction was thought to be due to lower expression of RT relative to Env and Gag
- CTL can lyse infected cells early after infection, possibly prior to viral production

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A2)	[Yang (1997a)]

- Epitope name: SL9. CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*
- CTL produced HIV-1-suppressive soluble factors – MIP-1α, MIP-1β, RANTES, after antigen-specific activation
- CTL suppress HIV replication more efficiently in HLA-matched cells

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p17(77–85)	p17(77–85 LAI)	SLYNTVATL	HIV-1 infection	human(A2)	[Parker (1992), Parker (1994)]

- Epitope name: SL9. Examined in the context of motifs important for HLA-A2 binding

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p17(77–85)	p17(77–85 LAI)	SLYNTVATL	HIV-1 infection	human(A2)	[McMichael & Walker(1994)]

- Epitope name: SL9. Review of HIV CTL epitopes

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A2)	[Tsomides (1994)]

- Epitope name: SL9. CTL clones recognize naturally processed peptide

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p17(77–85)	p17(77–85)	SLYNTVATL	*in vitro* stimulation	human(A2)	[Stuhler & Schlossman(1997)]

- Epitope name: SL9. A three cell-type cluster consisting of APCs, Th, and CTLs is the minimal regulatory unit required for Th cell-dependent induction of CTLs

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A2)	[Cao (1997)]

- Epitope name: SL9. The consensus peptides of B and D clade viruses and some Cs have the sequence SLYNTVATL
- The consensus peptide of A, and some C strains have SLFNTVATL, a form that is cross-reactive

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p17(77–85)	Gag(77–85)	SLYNTVATL	HIV-1 infection	human(A2)	[Dyer (1999)]

- Epitope name: SL9. CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A2)	[Harrer (1998)]

- Epitope name: SL9. Two overlapping epitopes were recognized in a long-term survivor, restricted by two different HLA molecules, HLA-A11(TLYCVHQR) and -A2 (SLYNTVATL)
- Viral sequence substitutions were present in this individual which did not affect viral replication and did not alter CTL-recognition of the A2 epitope, but reduced recognition of the A11 epitope, indicative of immune escape

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p17(77–85)	p17(77–85 SF2)	SLYNTVATL	HIV-1 infection	human(A2)	[Altfeld (2001a)]

- The relative contribution of CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells
- The A2 epitopes Vpr AIIRLLQQL and p17 SLYNTVATL do not account for the dominance of Vpr and p17, the result holds even when HLA-A2+ individuals are excluded

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p17(77–85)	p17( )	SLYNTVATL	*in vitro* stimulation	human(A2)	[Buseyne (2001)]

- Epitope name: SL9. Exogenous presentation or cross-presentation of epitopes by antigen presenting cells (APC) without protein synthesis is an alternative pathway for CTL epitope processing that may be important in the initial generation of viral specific CTL
- Dendritic cells treated with AZT to inhibit protein synthesis were able to elicit a strong specific CTL response in SLYNTVATL specific CTL line EM71-1 without protein synthesis, while macrophages demonstrated a decreased presentation efficiency
- Exogenous Gag epitope presentation was Env-dependent and required receptor-dependent fusion

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p17(77–85)	p17( )	SLYNVATL	HIV-1 infection	human(A2)	[Kostense (2001)]

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional

- In 15 of the patients, the proportion of IFNγ producing tetramer cells correlated with AIDS-free survival
- In one patient with a SLYNVATL response, no SLYNVATL mutations were found among 21 clones despite high viral load (260,000 RNA copies/ml serum), suggesting low *in vivo* efficacy of the SLYNVATL response

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A2)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p17(77–85)	p17( )	SLYNVATL	HIV-1 infection	human(A2)	[Seth (2001)]

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized
- 6/10 A*0201+ individuals had HIV-specific tetramer staining cells, and 5 of these declined upon successful therapy
- 4/10 A*0201+ individuals with chronic HIV-1 infection recognized this epitope
- Prior to therapy, the mean percentage of CD8+ cells that recognized the immunodominant epitope SLYNVATL was six-fold greater than the percentage recognizing the epitope ILKEPVHGV

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p17(77–85)	p17(77–85)	SLYNTVATL	HIV-1 infection	human(A2)	[Islam (2001)]

- Epitope name: SL9. Transcript frequencies were followed for four CTL clones from patient 115, with a chronic and stable HIV-1 infection, were tracked in a longitudinal study of samples collected 6-11 years post infection: clone M21 and E15 recognize ERYLKDQQL,and clone D87 recognizes variant ERYLQDQQL, and clone p175b recognizes the A2 epitope SLYNTVATL
- This epitope sequence from clone p175b uses the Vβ5, CDR3 (FDS), Jβ2.7 TCR β gene
- Responses were stable even through HAART with undetectable viral loads, but frequencies varied over time by 100-fold, ranging from 0.012% of the total population for SLYNTVATL at its lowest point to 3.78% for M21, with the relative frequencies of clones shifting over time

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p17(77–85)	p17(77–85 SF2)	SLYNTVATL	HIV-1 infection	human(A2)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 2/6 group 2, and 2/4 group 3

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p17(77–85)	p17(77–85)	SLFNTVATL	HIV-1 exposed seronegative, HIV-1 infection	human(A2)	[Kaul (2001a)]

- Variants SL(F/Y)NTVATL are A/B clade specific

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-A2 women, 1/10 HEPS and 22/26 HIV-1-infected women recognized this epitope, likelihood ratio 18.3, p value < 0.003, and ILK(D/E)PVHGV tended to be more reactive in HEPS women, SL(F/Y)NTVATL in infected women
- The dominant response to this HLA allele was to this epitope in the 1/10 HEPS cases and in 18 of the 22/26 HIV-1-infected women that responded
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort
- Subject ML 1250 had an A2 response to ILKD/EPVHGV prior to seroconversion, which switched to SLF/YNTVATL post-seroconversion
- Subjects ML 1575 and ML 1592 had no response to SLF/YNTVATL prior to seroconversion, but made responses post-seroconversion
- Subject ML 1760 had an A2 response to ILKD/EPVHGV prior to seroconversion, and gained responses to epitopes A2 SLF/YNTVATL and B27 KRWIIL/MGLNK post-seroconversion

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p17(77–85) p17(77–85 93TH253 CRF01) SLYNTIATL HIV-1 infection human(A2) [Sriwanthana (2001)]

- Epitope name: G77-85. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was reactive in HIV+ control study subjects 125 and 144 who carried HLA-A2

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p17(77–85) p17(77–85 93TH253 CRF01) SLYNTIATL HIV-1 infection human(A2) [Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested
- 2/4 tested FSWs recognized the E clade version of this epitope, SLYNTIATL, the B clade version is SLYNTVATL
- This epitope was only conserved in CRF01 and subtypes B and D, and exact matches were uncommon

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p17(77–85) p17(77–85) SLYNTVATL HIV-1 infection human(A2) [Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)

- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- SLYNTVATL was the dominant A2 epitope recognized in patients with chronic infection, except for Subject 11841 who recognized 5/8 epitopes
- Three subjects only had an A2 response to SLYNTVATL
- The two subjects with acute infection did not respond to SLYNTVATL

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p17(77–85) p17(77–85) SLYNTVATL HIV-1 infection human(A2) [Goulder (2001d)]

- Epitope name: SL9. Immune escape variants in this epitope where transmitted both horizontally and vertically in two families
- Eight transmitting mothers and 14 non-transmitters mothers were studied and variation within the SL9 epitope was associated carrying HLA-A2 (P=0.04), but no link between variation from the SL9 consensus and vertical transmission was established

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p17(77–85) p17( ) SLYNTVATL HIV-1 infection human(A2) [Altfeld (2000)]

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined

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p17(77–85) p17( ) SLYNTVATL HIV-1 exposed seronegative human(A2, A*0202) [Rowland-Jones (1998b)]

- Epitope name: SL9. HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among B and D clade viruses
- The clade A version of the epitope, SLFNTVATL, was preferentially recognized by CTL
- This epitope was recognized by two different exposed seronegative prostitutes

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p17(77–85) p17( ) SLYNTVATL HIV-1 infection human(B*0201) [Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705

- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

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p17(77–85) p17(77–85) SLYNTVATL HIV-1 infection human(B62) [Goulder (1997a)]

- Epitope name: SL9. This paper is a review of CTL and immune evasion, but it presents a study of a shift from an HLA-A*0201 response to SLYNTVATL, to a B62 response to GLNKIVRMY
- As long as a strong CTL response to SLYNTVATL was evident, the epitope variants SLFNTVATL or SLYNTIATL dominated the viral population – eventually the CTL response to the index peptide became undetectable, the CTL response shifted to a focus on GLNKIVRMY, and the index peptide SLYNTVATL once again established itself as the dominant form

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p17(82–91) p17(82–91 93TH253 CRF01) IATLWCVHQR HIV-1 exposed seronegative, HIV-1 infection human(A11) [Sriwanthana (2001)]

- Epitope name: G82-91. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was weakly reactive in the HEPS study subject 265 who was HLA A2/A11
- This epitope was strongly reactive in HIV+ study subject 053 who carried HLA-A11

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p17(82–91) p17(82–91 93TH253 CRF01) IATLWCVHQR HIV-1 infection human(A11) [Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined
- 3/8 tested FSWs recognized this epitope
- This epitope was not conserved in other subtypes, and exact matches were uncommon

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p17(84–91) p17(83–91) TLYCVHQR HIV-1 infection human(A11) [Harrer (1998)]

- Two overlapping epitopes were recognized in a long-term survivor, restricted by two different HLA molecules, HLA-A11(TLYCVHQR) and -A2 (SLYNTVATL)
- Viral sequence substitutions were present in this individual which did not affect viral replication and did not alter CTL-recognition of the A2 epitope, but reduced recognition of the A11 epitope, indicative of immune escape
- A Q90E substitution resulted in a loss of the ability of the peptide to induce lysis, R91K substitution was still reactive, and R91Q substitution showed a reduced ability to stimulate lysis

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p17(84–92)	p17(84–92)	TLYCVHQRI	HIV-1 infection	human(A*1101)	[Brander & Goulder(2001)]
	• C. Brander notes that this is an A*1101 epitope				
p17(84–92)	p17(84–92)	TLYCVHQRI	HIV-1 infection	human(A11)	[Brander & Walker(1995)]
	• Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study				
p17(84–92)	p17(84–92)	TLYCVHQRI	HIV-1 infection	human(A11)	[Birk (1998)]
	• A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs				
p17(84–92)	p17(84–92)	TLYCVHQRI	HIV-1 infection	human(A11)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
p17(84–92)	p17(84–92 SF2)	TLYCVHQRI	HIV-1 infection	human(A11)	[Altfeld (2001c)]
	• Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection • The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef • Previously described and newly-defined optimal epitopes were tested for CTL response • Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 1/2 group 3				
p17(84–92)	p17(84–92)	TLYCVHQRI	HIV-1 exposed seronegative, HIV-1 infection	human(A11)	[Kaul (2001a)]
	• ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers				
p17(86–101)	p17( )	YCVHQRIEIKDTKEAL	HIV-1 infection	human( )	[Altfeld (2000)]
	• This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual • The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined				
p17(86–101)	p17( )	YCVHQRIEIKDTKEAL	HIV-1 infection	human( )	[Altfeld (2000)]
	• This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual • The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined				
p17(87–105)	p17(91–105 SF2)	CRIDVKDTKEALEKIE	HIV-1 infection	human( )	[Lieberman (1997b)]
	• CTL expanded *ex vivo* were later infused into HIV-1 infected patients				

p17(88–115)	p17(88–115 ARV)	VHQRIEIKDTKEALDK-IEEEQNKSKKKA	HIV-1 infection	human(A2)	[Achour (1990)]

- B cell epitope HGP-30 also serves as a CTL epitope

p17(88–115)	p17(88–115 ARV)	VHQRIEIKDTKEALDK-IEEEQNKSKKKA	Vaccine	murine BALB/c(H-2^d)	[Hamajima (1997)]

Vaccine: *Vector/type:* peptide *HIV component:* V3, HPG30, CD4BS *Stimulatory Agents:* IL-12

- B cell epitope HGP-30 also serves as a CTL epitope
- Vaccine combined HGP-30, V3 loop peptide variants, and CD4 binding site peptide
- IL-12 expression plasmid included with the vaccination enhanced the CTL response

p17(90–101)	p17( )	RIDVKDTKEAL	HIV-1 infection	human( )	[Goulder (2000a)]

- The CTL-dominant response was focused on this epitope in an HIV+ Haitian living in Boston, who was A23/68 B45/72 Cw2/16 – this epitope fell outside the most recognized peptides in the study
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

p17(91–105)	p17(91–105 SF2)	RIDVKDTKEALEKIE	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA-A3, A24, B8, B55

p17(92–101)	p17(92–101)	IEIKDTKEAL	HIV-1 infection	human(B*4001)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*4001 epitope

p17(92–101)	p17( )	IEIKDTKEAL	HIV-1 infection	human(B60)	[Wagner (1998a)]

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1 α and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules

p17(92–101)	p17(92–101 SF2)	IEIKDTKEAL	HIV-1 infection	human(B60)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection

	• The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef • Previously described and newly-defined optimal epitopes were tested for CTL response • Number of HLA-B60+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 1/1 group 2, and 0/0 group 3				
p17(92–101)	p17( )	IEIKDTKEAL	HIV-1 infection	human(B60(B*4001)	[Altfeld (2000)]
	• This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes • B60 is present in 10-20% of the Caucasoid and very common in Asian populations				
p17(92–101)	p17(92–101)	IEIKDTKEAL	HIV-1 infection	human(B60/B61)	[Day (2001)]
	• No immunodominant responses were detected to five B61-restricted epitopes tested • All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response				
p17(93–101)	p17( )	DVKDTKEAL	HIV-1 infection	human( )	[Goulder (2000a)]
	• The CTL-dominant response was focused on this epitope in an HIV+ Caucasian from Boston, who was A1/*0201 B8/63 Cw7/- – this epitope fell outside the most recognized peptides in the study • Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses • Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa				
p17(93–101)	p17(93–101)	EIKDTKEAL	Peptide-HLA interaction	human(B8)	[DiBrino (1994b)]
	• Examined in the context of motifs important for HLA-B8 binding, predicted epitope based on Achour *et al*.				
p17(93–101)	p17(93–101)	EIKDTKEAL	HIV-1 infection	human(B8)	[Birk (1998)]
	• A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs				
p17(93–101)	p17(93–101 LAI)	EIKDTKEAL		human(B8,B60)	[Brander & Walker(1997)]
	• Pers. Comm. from A. Trocha and S. Kalams to C. Brander and B. Walker				
p17(121–132)	p17(121–132 HXB2R)	DTGHSNQVSQNY	HIV-1 infection	human(A33)	[Buseyne (1993b)]
	• Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people				

p17(121–132)	Gag(121–132 LAI)	DTGHSNQVSQNY	HIV-1 infection	human(A33)	[Buseyne (1993a)]

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed cytotoxic activity against at least one HIV protein was detected in 70% of infected children
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures
- Patient EM17 (CDC P2A+C+D2) had a CTL response to two epitopes in Gag

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p17(124–132)	p17(124–132 SF2)	NSSKVSQNY	HIV-1 infection	human(B35)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 0/2 group 2, and 1/1 group 3

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p17(124–132)	p17(124–132 LAI)	NSSKVSQNY	HIV-1 or HIV-2 infection	human(B*3501)	[Brander & Goulder(2001)]

- Noted by Brander to be B*3501 epitope

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p17(124–132)	p17( )	NSSQVSQNY	HIV-1 infection	human(B*3501)	[Dorrell (2001)]

- The crystal structure of this epitope bound to HLA-B*3501 shows that a serine can fit into the B pocket, which is shared between B35 and B53, with the hydroxyl group of the P2 serine occupying a position almost identical to the P2 proline that was previously considered the anchor motif
- Novel B53 epitopes (DTINEEAAEW and QATQEVKNM) were defined in this study that showed that A and T can also serve as P2 anchor residues for the B pocket of HLA-B35 and B53 – while S, T, and P could all fit into the B pocket and form a hydrogen bond, A would not form a bond, so the authors propose compensatory interactions account for the high affinity of QATQEVKNM for B53

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p17(124–132)	p17( )	NSSKVSQNY	HIV-1 infection	human(B35)	[Seth (2001)]

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized

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p17(124–132)	p17(124–132 LAI)	NSSKVSQNY	HIV-1 infection	human(B35)	[McMichael & Walker(1994)]

- Review of HIV CTL epitopes

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p17(124–132)	( )	NSSKVSQNY	HIV-1 infection	human(B35)	[Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found

- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

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p17(124–132) p17(124–132) NSSKVSQNY HIV-1 infection human(B35) [Birk (1998)]

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs

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p17(124–132) p17(124–132 LAI) NSSKVSQNY HIV-1 or HIV-2 infection human(B35) [Rowland-Jones (1995)]

- Established by titration

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p17(124–132) p17(124–132 LAI) NSSKVSQNY *in vitro* stimulation human(B35) [Lalvani (1997)]

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors

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p17(124–132) p17( ) NSSKVSQNY human(B35) [Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive
- HIV-2 version of this epitope is not conserved: PPSGKGGNY, but the CTLs are cross-reactive – this is one of five B35 CTL epitopes that are cross-reactive, see also [Rowland-Jones (1995)]

Table 2: **p17-p24**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
p17-p24(127–3)	p17-p24(127–135 clade D)	QVSQNYPIV		human(A*6802)	[Dong(1998)]
	• Epitope starts in p17 and ends in p24 • Predicted on binding motif, no truncations analyzed				
p17-p24(131–6)	p17-p24(132–140 SF2)	NYPIVQNL	HIV-1 infection	human(A*2402)	[Ikeda-Moore (1997)]
	• The epitope starts in p17 and ends in p24 • Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402 • This peptide induced CTL in 1/4 HIV-1+ people tested • NYPIVQNL bound to A*2402 with medium strength, and the epitope can be processed in a vaccinia construct and presented – no CTL clone was obtained				

Table 3: **p24**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
p24(8–17)	p24(140–149)	GQMVHQAISP	HIV-1 infection	human(B57)	[Betts (2000)]
• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant • Ninty fiveoptimally defined peptides from this database were used to screen for γ interferon responses to other epitopes • 1/11 of the A2+ individuals was HLA A*0201, A1, B57 and responded to four B57 epitopes and two others					
p24(8–20)	p24(140–152 IIIB)	GQMVHQAISPRTL	HIV-1 infection	human(Cw3)	[Littaua (1991)]
• Fine specificity of human Cw3 restricted Gag CTL epitope					
p24(8–27)	p24(140–159)	GQMVHQAISPRTLNA-WVKVV	HIV-1 infection	human(B14)	[Musey (1997)]
• CTL specific for this epitope were found in the peripheral blood but not in the cervical mucosa of one donor					
p24(9–18)	Gag(173–182)	QMVHQAISPR	HIV-1 infection	human(A3 supertype)	[Propato (2001)]
• Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes • Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs • A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus • This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)					
p24(10–18)	Gag(174–182)	MVHQAISPR	HIV-1 infection	human(A3 supertype)	[Propato (2001)]
• Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes • Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs • A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus • This epitope can bind 5/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)					
p24(11–24)	p24( )	VQHAISPRTLNAWV	HIV-1 infection	human( )	[Goulder (2000a)]
• The CTL-dominant response was focused on this epitope in an HIV+ Haitian living in Boston, who was A34/68 B57/71 Cw3/7 – this epitope fell outside the most recognized peptides in the study • Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses					

- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

p24(11–32)	p24(143–164 BH10)	VHQAISPRTLNAWVK-VVEEKAF	HIV-1 infection	human(Bw57)	[Johnson (1991)]

- Gag CTL response studied in three individuals

p24(12–20)	Gag(146–154)	HQAISPRTL	HIV-1 infection	chimpanzee(Patr-B*02)	[Balla-Jhagjhoorsingh (1999b)]

- Certain HLA-alleles have been associated with long-term survival – among them are HLA-B*27 and HLA-B*57
- Of more than 150 chimpanzees that have been reported to be infected with HIV-1, only one has developed AIDS
- CTL responses were studied in two HIV-1 infected chimpanzees that have strong CTL responses, and they responded to highly conserved epitopes that are recognized in humans in the context of HLA-B*27 and HLA-B*57
- The human HLA protein which presents this Patr-B*02 epitope is HLA-B*5701 but the amino acid sequences in the binding pockets of HLA-B*5701 and Patr-B*02 are distinctive

p24(13–20)	p24(145–152)	QAISPRTL	HIV-1 exposed seronegative, HIV-1 infection	human(Cw3)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

p24(13–23)	p24(145–155)	QAISPRTLNAW	HIV-1 infection	human( )	[Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninty five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- 1/11 of the A2+ individuals was HLA A*0201, A1, B57 and responded to QAISPRTLNAW noted previously to be A25

p24(13–23)	p24(145–155 LAI)	QAISPRTLNAW		human(A*2501)	[Brander & Goulder(2001)]

- C. Brander notes that this is an A*2501 (Pers. Comm. I. Kurane and K. West)

p24(13–23)	p24(145–155 SF2)	QAISPRTLNAV	HIV-1 infection	human(A25)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A25+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/2 group 2, and 1/3 group 3

p24(13–23)	p24(145–155 LAI)	QAISPRTLNAW		human(A5)	[Kurane & West(1998)]
p24(15–23)	( )	LSPRTLNAW	HIV-1 infection	human( )	[Kaul (2001b)]
	• This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative • The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire • ISPRTLNAW was consistently recognized by one of 22 HEPS sex worker controls (ML1250), and LSPRTLNAW was recognized by two additional HEPS sexworker control (ML1693 and ML1589)				
p24(15–23)	p24(147–155 IIIB)	ISPRTLNAW	HIV-1 infection	human(B*5701)	[Brander & Goulder(2001)]
	• C. Brander notes this is a B*5701 epitope				
p24(15–23)	Gag(147–155 LAI)	ISPRTLNAW	HIV-1 infection	human(B*5701 B*5801)	[Klein (1998)]
	• B57 has been associated with long-term non-progression in the Amsterdam cohort • The most pronounced CTL responses in HLA B*5701 LTS were to RT and Gag				
p24(15–23)	p24(147–155)	ISPRTLNAW	HIV-1 infection	human(B57)	[Betts (2000)]
	• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant • Ninty five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes • 1/11 of the A2+ individuals was HLA A*0201, A1, B57 and responded to four B57 epitopes and two others, but not SLYNTVATLjt				
p24(15–23)	Gag( )	ISPRTLNAW	HIV-1 infection	human(B57)	[Goulder (2001b)]
	• Epitope name: IW9. This epitope elicited the second strongest CTL response in patient PI004 during acute infection, and maintained the response • Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond				
p24(15–23)	p24(147–155)	ISPRTLNAW	HIV-1 infection	human(B57)	[Oxenius (2000)]
	• Epitope name: ISP. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable • None of the 8 study subjects recognized this epitope but none were HLA B57+				
p24(15–23)	p24(15–23)	ISPRTLNAW	HIV-1 infection	human(B57)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				

p24(15–23)	p24(147–155 SF2)	ISPRTLNAW	HIV-1 infection	human(B57)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 2/2 group 3

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p24(15–23)	p24(147–155 IIIB)	ISPRTLNAW	HIV-1 infection	human(B57,B*5801)	[Goulder (1996b)]

- Five slow progressors made a response to this epitope, and in two it was the dominant response
- Peptide defined on the basis of B*5801 binding motif, yet not cross-restricted except at high concentrations

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p24(15–23)	p24( )	LSPRTLNAW	HIV-1 exposed seronegative	human(B57,B58)	[Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells
- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women

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p24(15–23)	p24(147–155)	LSPRTLNAW	HIV-1 exposed seronegative, HIV-1 infection	human(B57,B58)	[Kaul (2001a)]

- Variants (L/I)SPRTLNAW are specific for the A/B clades
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B57/B58 women, 4/6 HEPS and 14/17 HIV-1-infected women recognized this epitope
- The dominant response to this HLA allele was to this epitope in 2 of the 4/6 HEPS cases and in 7 of the 14/17 responsive HIV-1-infected women

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p24(16–24)	p24( )	SPRTLNAWV	HIV-1 infection	chimpanzee( )	[Santra (1999)]

- 3/4 animals displayed HIV-1 Gag-specific CTL activity
- Effector cells from two chimpanzees were able to recognize epitopes also recognized by human HIV-1 Gag-specific CTL (SPRTLNAWV, HLA-B7, and DLNTMLNTV, HLA-B14)

- No chimpanzee CTL were detected to the following human HIV-1 specific Gag epitopes, although they were embedded within 20mer peptides that contained a reactive epitope: ISPRTLNAW, HLA-B57; KRWIILGLNK, HLA-B27; and DRFYKTLRA, HLA-B14

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p24(16–24) p24(148–156) SPRTLNAWV human(B*0702) [Brander & Goulder(2001)]

- C. Brander notes this is a B*0702 epitope
- Optimal peptide mapped by titration, Pers. Comm. from D. Lewinsohn to C. Brander and B. Walker

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p24(16–24) p24(148–156) SPRTLNAWV human(B7) [Brander & Walker(1997)]

- Optimal peptide mapped by titration, Pers. Comm. from D. Lewinsohn to C. Brander and B. Walker

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p24(16–24) p24(148–156) SPRTLNAWV HIV-1 infection human(B7) [Brodie (2000)]

- Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1α and MIP-1β, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*

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p24(16–24) p24(148–156) SPRTLNAWV HIV-1 exposed seronegative, HIV-1 infection human(B7) [Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV

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p24(16–24) p24(16–24) SPRTLNAWV HIV-1 infection human(B7) [Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested

	• The B7-restricted CTL response was highly variable and there was no clearly dominant epitope				
p24(16–24)	p24( )	SPRTLNAWV	HIV-1 exposed seronegative	human(B7,B*8101)	[Kaul (2000)]
	• 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses • Low risk individuals did not have such CD8+ cells • CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women				
p24(16–24)	Gag( )	SPRTLNAWV	HIV-1 exposed seronegative	human(B7,B*8101)	[Rowland-Jones (1998b)]
	• HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection • Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world • Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes • This epitope is conserved among A, B, and D clade viruses				
p24(19–27)	p24(151–159)	TLNAWVKVV	HIV-1 infection	human(A*02)	[Huang (2000)]
	• The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed • Increases in γ interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-γ-production ELISPOT • In 3/3 HLA-A*02 B*27 subjects the immunodominant epitope was against HLA B*27 Gag p24 epitope KRWIILGL, not A2 Gag epitopes				
p24(19–27)	p24(151–159)	TLNAWVKVV	HIV-1 infection	human(A*02)	[Rinaldo (2000)]
	• Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that can persist after therapy and long periods of virus being below the level of detection				
p24(19–27)	p24(151–159)	TLNAWVKVV	HIV-1 infection	human(A2)	[Parker (1992), Parker (1994)]
	• Study of sequence motifs preferred for peptide binding to class I HLA-A2				
p24(19–27)	p24(19–27)	TLNAWVKVV	HIV-1 infection	human(A2)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
p24(19–27)	p24(150–159)	TLNAWVKVI	HIV-1 exposed seronegative, HIV-1 infection	human(A2)	[Kaul (2001a)]
	• Variants TLNAWVKV(I/V) are A/B clade specific • ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers				

p24(19–27)	p24( )	TLNAWVKVV	HIV-1 exposed seronegative	human(A2, A*0202)	[Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among A, B and D clade viruses

p24(21–40)	p24(153–172 SF2)	NAWVKVVEEKAFSPE-VIPMF	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA-A2, B21

p24(21–40)	p24(153–172 SF2)	NAWVKVVEEKAFSPE-VIPMF	Vaccine	Rhesus macaque( )	[Wagner (1998b)]

Vaccine: *Vector/type:* virus-like particle *HIV component:* gag, gp120, V3, CD4BS

- A VLP is a non-infectious virus-like particle self-assembled from HIV Pr55 gag – macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains Gag and Env specific CTL were stimulated in each case, and Ab response to gag and gp120 was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4 – despite the CTL and Ab response, immunized macaques were infected by intervenous challenge with SHIV chimeric challenge stock [Wagner (1998b)]
- CTL specific for this epitope could be found both before and after SHIV challenge

p24(21–40)	Gag(153–172)	NAWVKVVEEKAFSPE-VIPMF	HIV-1 infection	human(B57)	[Brodie (1999)]

- The ability of CTL effector cells was studied by expanding autologous HIV-1 Gag-specific CTL *in vitro*, and adoptively transferring them
- The transferred CTLs migrated to the lymph nodes and transiently reduced circulating productively infected CD4+ T-cells, showing that CTL move to appropriate target sites and mediate anti-viral effects

p24(21–40)	p24(153–172)	NAWVKVVEEKAFSPE-VIPMF	HIV-1 infection	human(B57)	[Brodie (2000)]

- Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, co-localizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1α and MIP-1β, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*

p24(21–42)	p24(153–174 BH10)	NAWVKVVEEKAFSPE-VIPMFSA	HIV-1 infection	human(Bw57)	[Johnson (1991)]
• Gag CTL response studied in three individuals					
p24(28–47)	p24(160–179)	EEKAFSPEVIPMFSALS-EGA	HIV-1 infection	human(B27)	[Musey (1997)]
• Cervical and peripheral blood derived CTL clones from an HIV-infected woman recognized this epitope					
p24(30–37)	p24(162–170 LAI)	KAFSPEVI	HIV-1 infection	human(B*5703)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*5703 epitope					
p24(30–37)	p24(30–37)	KAFSPEVI	HIV-1 infection	human(B57)	[Goulder (2000c)]
• Two strong clonal CTL responses were generated in donor 026-BMC (HLA A3/-, B42/B57, Cw7/17) against different optimal versions of this epitope, one 8 amino acids long, one 11					
• Improved stabilization of the B57-peptide complex was demonstrated by the 11 mer which fits the B57 binding motif, relative to the 8 mer, which does not					
• B57 tolerates marked difference in optimal peptide length – and B57 is associated with non-progressive infection					
p24(30–39)	p24( )	KAFSPEVIPMF	HIV-1 infection	human( )	[Kaul (2001b)]
• This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative					
• The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire					
• This epitope was recognized by 1/22 HEPS sex worker controls, ML1250					
p24(30–40)	p24( )	KAFSPEVIPMF	HIV-1 infection	human(B*57)	[Spiegel (1999)]
• Study examines the effect of highly active antiretroviral therapy (HAART) on HIV-1 plasma viral load, CTLp and CTLe frequencies in 8 infected children					
• CTLp (precursors) were measured by stimulating in culture and assaying using 51Cr release, against vaccina expressed IIIB Env, Gag, Pol, Nef, and CTLe were measured by ELISPOT					
• CTL against B*57-KAFSPEVIPMF was a de novo response observed in one of the children when viral load increased as a result of stopping therapy					
• HIV-1 specific CTL responses initially increased in children with complete viral suppression, but then decreased, suggesting viral replication is needed to maintain CTL responses					
p24(30–40)	p24(162–172 LAI)	KAFSPEVIPMF	HIV-1 infection	human(B*5701)	[Goulder (1996b)]
• This peptide was recognized by CTL from five slow progressors					
• Peptide defined on the basis of B*5801 binding motif, yet not cross-restricted except at high concentrations					
• This epitope is highly conserved					

p24(30–40)	p24(162–172 LAI)	KAFSPEVIPMF	HIV-1 infection	human(B*5701)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*5701 epitope					
p24(30–40)	p24(162–172 LAI)	KAFSPEVIPMF	HIV-1 infection	human(B*5703)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*5703 epitope					
p24(30–40)	p24(30–40)	KAFSPEVIPMF	HIV-1 infection	human(B57)	[Goulder (2000c)]
• Two strong clonal CTL responses were generated in donor 026-BMC (HLA A3/-, B42/B57, Cw7/17) against different optimal versions of this epitope, one 8 amino acids long, one 11					
• Improved stabilization of the B57-peptide complex was demonstrated by the 11mer which fits the B57 binding motif, relative to the 8 mer, which does not					
• B57 tolerates marked difference in optimal peptide length – and B57 is associated with non-progressive infection					
p24(30–40)	p24(162–172)	KAFSPEVIPMF	HIV-1 infection	human(B57)	[Betts (2000)]
• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant					
• Ninty five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes					
• 1/11 of the A2+ individuals was HLA A*0201, A1, B57 and responded to four B57 epitopes and two others					
p24(30–40)	p24( )	KAFSPEVIPMF	HIV-1 infection	human(B57)	[Goulder (2000a)]
• The CTL-dominant response was focused on this epitope in an HIV+ Caucasian living in Boston – this epitope is not among the most recognized peptides in the study					
• Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses					
• Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa					
p24(30–40)	Gag( )	KAFSPEVIPMF	HIV-1 infection	human(B57)	[Goulder (2001b)]
• Epitope name: KF11. Three CTL responses in patient PI004, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond					
p24(30–40)	p24(162–172)	KAFSPEVIPMF	HIV-1 infection	human(B57)	[Oxenius (2000)]
• Epitope name: KAF. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable					
• None of the 8 study subjects recognized this epitope but none were HLA B57+					

p24(30–40)	p24( )	KAFSPEVIPMF	HIV-1 infection	human(B57)	[Kostense (2001)]

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional
- In 15 of the patients, the proportion of IFNγ producing tetramer cells correlated with AIDS-free survival

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p24(30–40)	p24(162–172 SF2)	KAFSPEVIPMF	HIV-1 infection	human(B57)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 2/2 group 3

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p24(30–40)	p24(163–174)	KAFSPEVIPMF	HIV-1 infection	human(B57)	[Appay (2000)]

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV
- HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

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p24(30–40)	p24(153–164)	KAFSPEVIPMF	HIV-1 exposed seronegative, HIV-1 infection	human(B57,B58)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B57/B58 women, 4/6 HEPS and 12/17 HIV-1-infected women recognized this epitope
- The dominant response to this HLA allele was to this epitope in 2 of the 4/6 HEPS cases and in 7 of the 12/17 HIV-1-infected women

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p24(30–40)	p24(30–40)	KAFSPEVIPMF	HIV-1 infection	human(B58)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p24(31–50)	p24(163–182)	AFSPEVIPMFSALSEG-ATPQ	HIV-1 infection	human( )	[Lieberman (1995)]
• HIV-specific CTL lines developed by *ex vivo* stimulation with peptide					
p24(31–50)	p24(163–182 SF2)	AFSPEVIPMFSALSEG-ATPQ	HIV-1 infection	human( )	[Lieberman (1997a)]
• Of 25 patients, most had CTL specific for more than one HIV-1 protein • Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag • One of these 12 had CTL response to this peptide • The responding subject was HLA-A2, B21					
p24(31–50)	p24(163–182 SF2)	AFSPEVIPMFSALSEG-ATPQ	HIV-1 infection	human( )	[Lieberman (1997b)]
• CTL expanded *ex vivo* were later infused into HIV-1 infected patients					
p24(31–50)	p24( )	AFSPEVIPMFSALSEG-ATPQ	HIV-1 infection	human( )	[Altfeld (2000)]
• This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual • The response to the peptide was CD4 dependent, but the HLA presenting molecule and optimal epitope were not determined					
p24(35–43)	p24(167–175 LAI)	EVIPMFSAL		human(A*2601)	[Goulder (1996a)]
• Identified as optimal epitope within Gag sequence AFSPEVIPMFSALSEGATPQ • Relatively conserved epitope within B clade and in other clades • Suspected binding motif for HLA-A26 includes T or V anchor at position 2, negative charge at position 1 • C. Brander notes that this is an A*2601 epitope in the 1999 database					
p24(35–43)	p24(167–175 LAI)	EVIPMFSAL		human(A*2601)	[Brander & Goulder(2001)]
• C. Brander notes that this is an A*2601					
p24(35–43)	p24(167–175)	EVIPMFSAL	HIV-1 infection	human(A26)	[Betts (2000)]
• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant • Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes • 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope					
p24(36–43)	p24(168–175 LAI)	VIPMFSAL		human(C*0102(Cw1))	[Brander & Goulder(2001)]
• C. Brander notes this is a C*0102(Cw1) epitope					
p24(36–43)	p24(168–175 LAI)	VIPMFSAL		human(Cw*0102,Cw1)	[Goulder (1997b)]

p24(36–43)	p24(168–175)	VIPMFSAL	HIV-1 infection	human(Cw01,02)	[Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope

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p24(37–52)	Gag(169–184 LAI)	IPMFSALSEGATPQDL	HIV-1 infection	human(B12)	[Buseyne (1993a)]

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed cytotoxic activity against at least one HIV protein was detected in 70% of infected children
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures
- Patient EM17 (CDC P2A+C+D2) had a CTL response to two epitopes in Gag

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p24(37–52)	p24(169–184 LAI)	IPMFSALSEGATPQDL	HIV-1 infection	human(B12(44))	[Buseyne (1993b)]

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people

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p24(37–52)	p24(37–52)	IPMFSALSEGATPDQL	HIV-1 infection	human(B44)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p24(41–60)	p24(173–192 SF2)	SALSEGATPQDLNTML-NTVG	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- Three of these 12 had CTL response to this peptide
- The responding subjects were HLA-A3, A32, B7, B14; and HLA-A2, A3, B14, B44

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p24(41–60)	p24(173–192 SF2)	SALSEGATPQDLNTML-NTVG	HIV-1 infection	human( )	[Lieberman (1997b)]

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients

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p24(41–60)	p24( )	SALSEGATPQDLNTML-NTVG	HIV-1 infection	human( )	[Altfeld (2000)]

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined

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p24(41–60)	p24(179–188 clade A)	SALSEGATPQDLNMM-LNIVG	HIV-1 infection	human(B*8101)	[Dorrell (1999)]

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa

	• This CTL epitope is presented by B*8101 in one of the patients with an A subtype infection – B*8101 is a newly discovered HLA allele found in Africans, and the epitope has yet to be mapped precisely • This epitope is distinct in subtype A relative to subtypes B, C, and D which share the dominant sequence: SALSEGATPQDLNTML-NTVG				
p24(41–62)	p24(173–194 BH10)	SALSEGATPQDLNTML-NTVGGH	HIV-1 infection	human(B14)	[Johnson (1991)]
	• Gag CTL response studied in three individuals				
p24(43–52)	p24( )	LSEGATPQDL	HIV-1 infection	human(B42,B44)	[Cao (2000)]
	• HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D • Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype • This optimal epitope sequence, recognized by CTL derived from a Ugandan with an A subtype infection (patient SP 511), is cross-reactive with subtypes A, B and D peptides				
p24(44–52)	p24(176–184)	SEGATPQDL		human(B*4001)	[Brander & Goulder(2001)]
	• C. Brander notes this is a B*4001, B60 epitope (Pers. Comm. A. Trocha and S. Kalams)				
p24(44–52)	p24( )	SEGATPQDL	HIV-1 infection	human(B60(B*4001)	[Altfeld (2000)]
	• This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes • B60 is present in 10-20% of the Caucasoid and very common in Asian populations				
p24(44–52)	p24(44–52)	SEGATPQDL	HIV-1 infection	human(B60/B61)	[Day (2001)]
	• No immunodominant responses were detected to five B61-restricted epitopes tested • All five B60-restricted epitopes were reactive in another subject, the strongest CTL response directed against the B60-epitope p24 SEGATPQDL, and the B60-restricted responses together contributed over one-third of the total CTL response				
p24(46–59)	p24( )	GATPQDLNTMLNTV	HIV-1 infection	human( )	[Goulder (2000a)]
	• The CTL-dominant response was focused on this epitope in an HIV+ African American living in Boston with HLA A*3002/68 B14/*5802 Cw6/8 – this epitope fell within the most recognized peptides in the study • Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses • Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa				

p24(47–55)	p24(47–55)	ATPQDLNTM	HIV-1 infection	human(B7)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

p24(47–56)	p24( )	ATPQDLNMML	HIV-1 exposed seronegative	human(B53)	[Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells
- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women

p24(47–58)	p24(181–192)	CTPYDINQMLNC	HIV-2 infection	human(B58)	[Bertoletti(1998)]

- HIV-2 epitope defined from an infection in Gambia, Bertoletti, Pers. Comm.

p24(48–56)	Gag( )	TPQDLNTML		human(A*4201,B*8101)	[Novitsky (2001)]

- Epitope name: G180-TL9. This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort
- 19/46 (41.3%) had CTL responses to one or more peptides within the first immunodominant region of Gag (peptides TL-NAWVKVIEEKAFSPEVIP, EKAFSPEVIPMFTALSEGAT, and MFTALSEGATPQDLNTMLNT), with magnitudes of response with ELISPOT results median and range 495 (103 to 1,447) SFC/10^6 PBMC
- 7/11 HLA-A*4201+ subjects (64%) responded to peptide MFTALSEGATPQDLNTMLNT
- TPQDLNTML is an A*4201 epitope within TLNAWVKVIEEKAFSPEVIP

p24(48–56)	p24(180–188 IIIB)	TPQDLNTML	HIV-1 infection	human(B*0702)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*0702 epitope

p24(48–56)	p24(179–187 LAI)	TPQDLNTML		human(B*4201)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*4201 epitope

p24(48–56)	Gag(173–181 HIV-2)	TPYDINQML	HIV-2 infection	human(B*5301)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*5301 epitope

p24(48–56)	p24(180–188 LAI)	TPQDLNTML	HIV-1 infection	human(B*8101)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*8101 epitope

p24(48–56)	Gag(180–188 HXB2)	TPQDLNTML	HIV-1 infection	human(B*8101)	[Mulligan (2001)]

- Epitope G18 from Patient 02110 with HLA genotypes A*3402, A*7401, B*5301, B*8101, Cw*0401, Cw*0802

p24(48–56)	p24( )	TPQDLNTML	HIV-1 infection	human(B42)	[Goulder (2000a)]

- B42 and B81 are very similar, and both can present this epitope to B42-positive effector cells – this epitope is almost certainly optimal for B81 as well – B42 and or B81 are expressed in 40-45% of Zulu and Xhosa infected individuals in South Africa, and in 14/18 B42 or B81+ individuals, the dominant gag response was to TPQDLNTML

	• Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses • Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects.				
p24(48–56)	Gag( )	TPQDLNTML	HIV-1 infection	human(B42)	[Goulder (2000b)]
	• Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA]) • HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection				
p24(48–56)	p24( )	TPQDLNQML		human(B53)	[Rowland-Jones (1999)]
	• CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5 • In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective • HIV-2 sequence: TPYDINQML, no cross-reactivity, [Gotch (1993)]				
p24(48–56)	Gag(173–181 HIV-2)	TPYDINQML	HIV-2 infection	human(B53)	[Gotch (1993)]
p24(48–56)	Gag(180–188 subtype A)	TPQDLNMML	HIV-1 infection, *in vitro* stimulation	human(B53)	[Dorrell (2001)]
	• In vitro restimulation of CTL specific for dominant epitopes from infected individuals is possible using recombinant modified vaccinia virus Ankara (MVA) carrying A or D subtype HIV-1 Gag proteins				
p24(48–56)	p24(180–188 subtype A consensus)	TPQDLNMML	HIV-1 infection	human(B53)	[Dorrell (2001)]
	• In clade A infected Gambians, three HLA-B53 epitopes were defined in Gag p24 using ELISPOT, tetramer, and cytotoxicity assays • This optimal epitope was identified within the 20 mer reactive peptide that carried it by homology with a B53 epitope from HIV-2, a B subtype B7 peptide that corresponds to it, as B53 is part of the B7 superfamily, and by the proline in the anchor at position 2 • TPQDLNMML was recognized in 6/7 HLA-B53 subjects and was immunodominant in most subjects • TPQDLNMML was A subtype-specific with no cross-recognition of the subtype B, C, and D variant, TPQDLNTML, although the B/C/D variant bound more efficiently to B53 • Position 7 showed great positional variation in crystal structures of two HLA-B53 complexes, suggesting variation here might significantly alter the position of the peptide in the binding groove and thus affect TCR interactions • Only one subject might have had a cross-reactive response with the HIV-2 and Mamu-A*01 variant CTPYDINQML, and this subject might have been dual infected with HIV-2				

p24(48–56)	p24(180–188 IIIB)	TPQDLNTML	HIV-1 infection	human(B7)	[Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- No variants of this epitope were found in a non-transmitting mother that had a CTL response to this epitope

p24(48–56)	p24(180–188)	TPQDLNTML	HIV-1 infection	human(B7)	[Jin (2000b)]

- This is the optimal epitope for the immunodominant response defined using a conventional approach in an HLA B7+ long-term non-progressor
- Three additional sub-dominant HLA B7 epitopes were defined using EpiMatrix, a non-anchor based strategy for defining potential epitopes, which highlighted 2078 possible epitopes in the autologous HIV-1 derived from the study subject – this was followed by B7 anchor residue prediction which narrowed the set to 55 peptides, three of which could serve as functional CTL epitopes

p24(48–56)	p24( )	TPQDLNTML	HIV-1 infection	human(B7)	[Goulder (2001b)]

- Epitope name: TL9. Recognized by patient 9354 during chronic infection, used as a positive control in a study of the SLYNTVATL epitope

p24(48–56)	p24(48–56)	TPQDLNTML	HIV-1 infection	human(B7)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope

p24(48–56)	p24(180–188 LAI)	TPQDLNTML	HIV-1 infection	human(C*0802(Cw8))	[Brander & Goulder(2001)]

- C. Brander notes this is a C*0802(Cw8) epitope

p24(48–57)	Gag( )	TPQDLNMMLN		human(B7)	[De Groot (2001)]

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay
- TPQDLNMMLN was newly-defined as an HLA-B7 epitope in this study, athough it was previously published as a B*8101 epitope
- TPQDLNMMLN was shown to stimulate an ELISPOT response, but could not be shown to bind to HLA-B7
- The variant TPQDLNTMLN was cross-reactive, had previously been identified as a HLA-B14 epitope, and could bind to HLA-B7

p24(49–57)	p24(181–189 LAI)	PQDLNTMLN	HIV-1 infection	human(B14, Cw8)	[Lubaki (1997)]

- Eighty-two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response
- Despite this being a well defined conserved epitope, none of the 11 gag-specific clones from a B-14 positive subject could recognize either it or p24 RAEQASQEV
- Christian Brander notes that B14 and Cw8 are in linkage disequilibrium, and that this epitope may be Cw8

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p24(51–59)	p24( )	DLNTMLNTV	HIV-1 infection	chimpanzee( )	[Santra (1999)]

- 3/4 animals displayed HIV-1 Gag-specific CTL activity
- Effector cells from two chimpanzees were able to recognize two epitopes also recognized by human HIV-1 Gag-specific CTL (SPRTLNAWV, HLA-B7, and DLNTMLNTV, HLA-B14)
- No chimpanzee CTL were detected to the following human HIV-1 specific Gag epitopes, although they were embedded within 20mer peptides that contained a reactive epitope: ISPRTLNAW, HLA-B57; KRWIILGLNK, HLA-B27; and DRFYKTLRA, HLA-B14

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p24(51–59)	p24( )	DLNMMLNIV	HIV-1 exposed seronegative	human(B14)	[Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells
- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women

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p24(51–59)	p24( )	DLNMMLNIV	HIV-1 infection	human(B14)	[Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized in 1/22 HEPS sex worker controls, ML1792

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p24(51–59)	p24(183–191 LAI)	DLNTMLNTV	HIV-1 infection	human(B14)	[Mollet (2000)]

- Epitope name: G5. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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p24(51–59)	p24(183–191)	DLNMMLNIV	HIV-1 exposed seronegative, HIV-1 infection	human(B14)	[Kaul (2001a)]

- Variants DLNMMLNIV/DLNTMLNVV are specific for clades A/B
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B14 women, 4/4 HEPS and 3/7 HIV-1-infected women recognized this epitope, likelihood ratio 4.8, p value 0.1, and HEPS women tended to respond to DLNMMLNIV/DLNTMLNVV, while infected women tended to respond to DRF(F/W)KTLRA
- The dominant response to this HLA allele was to this epitope for all 4/4 HEPS cases and in only one of the 3/7 HIV-1-infected women
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort
- Four epitopes were considered to be “resistant epitopes”, as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILKD/EPVHGV in RT, A*6802 DTVLEDINL in Protease, B14 DLNM/TLNI/VV in p24 and B18 FRDYVDRFY/FK also in p24

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p24(51–59)	p24(183–191 LAI)	DLNTMLNTV	HIV-1 infection	human(B14, Cw8)	[Johnson (1992), Nixon (1988)]

- Recent evidence indicates this is a Cw8 epitope; B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication)

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p24(51–59)	p24( )	DLNTMLNTV	HIV-1 exposed seronegative	human(B14, Cw8)	[Rowland-Jones (1998a)]

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating
- The A subtype consensus is identical to the B clade epitope
- The D subtype consensus is dLNmMLNiV
- Recent evidence indicates this is a Cw8 epitope; B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication)

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p24(51–59)	p24(183–191 LAI)	DLNTMLNTV	HIV-1 infection	human(C*0802)	[Brander & Goulder(2001)]

- C. Brander notes this is a C*0802 epitope

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p24(51–59)	p24(183–191 LAI)	DLNTMLNTV	HIV-1 infection	human(Cw8)	[McMichael & Walker(1994)]

- Review of HIV CTL epitopes – defined by B14 motif found within a larger peptide
- Recent evidence indicates this is a Cw8 epitope; B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication)

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p24(51–59)	p24( )	DLNTMLNTV	HIV-1 exposed seronegative	human(Cw8, B*1402)	[Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among B and D clade viruses
- The clade A version of the epitope, DLNNMLNIV, was preferentially recognized by CTL
- Recent evidence indicates this is a Cw8 epitope; B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication)

p24(51–70)	p24(183–202 SF2)	DLNTMLNTVGGHQAA-MQMLK	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA-A26, A30, B38

p24(51–82)	Gag(183–214 LAI)	DLNTMLNTVGGHQAA-MQMLKETINEEAAEWD-R	Vaccine	human( )	[Gahery-Segard (2000)]

Vaccine: *Vector/type:* lipopeptide *HIV component:* six peptides

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 2/10 reacted to this peptide
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual
- None of the 12 tested had an IgG response to this peptide

p24(61–69)	p24(193–201 LAI)	GHQAAMQML		human(B*3901)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*3901 epitope

p24(61–69)	p24(193–201 LAI)	GHQAAMQML		human(B39)	[Kurane & West(1998)]

- Optimal peptide defined by titration

p24(61–71)	p24(193–203 BRU)	GHQAAMQMLKE	HIV-1 infection	human(A2)	[Claverie (1988)]

- One of four epitopes first predicted, then shown to stimulate HLA-A2 restricted CTL line

p24(61–80)	p24(193–212 SF2)	GHQAAMQMKETINEE-AAEW	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA-A26, A30, B38

p24(61–82)	p24(193–214 BH10)	GHQAAMQMLKETINE-EAAEWDR	HIV-1 infection	human(Bw52)	[Johnson (1991)]

- Gag CTL response studied in three individuals

p24(62–70)	p24(194–202 LAI)	HQAAMQMLK		human(B52)	[Brander & Walker(1996)]

- P. Goulder, pers. comm.

p24(65–73)	p24(199–207 SF2)	AMQMLKETI	Vaccine	murine(H-2K^d)	[Doe & Walker(1997)]

Vaccine: *Vector/type:* vaccinia *HIV component:* Gag, Pol

- Immunodominant murine CTL response to this peptide observed after immunization with vaccine VVgagpol
- Optimal peptide was defined

p24(65–73)	Gag(197–205)	AMQMLKETI	Vaccine	murine(H-2K^d)	[Rayevskaya & Frankel(2001)]

Vaccine: *Vector/type:* Listeria monocytogenes *HIV component:* gag

- BALB/c mice were immunized with a highly attenuated recombinant Listeria monocytogenes, Lmdaldat, that can grow only when supplemented with D-alanine, and that expresses HIV-1 HXB2 Gag
- Parenteral immunization provided protection against systemic and mucosal challenges with a recombinant vaccinia virus expressing HIV-1 gag, and a long lasting memory CTL response against Gag in spleen, mesenteric lymph nodes, and Peyer's patches directed against the gag protein
- Oral immunization gave protection only against mucosal virus challenge and was associated with a transient CTL response in the three lymphoid tissues examined
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways

p24(65–73)	Gag(197–205 SF2)	AMQMLKETI	Vaccine	murine(H-2K^d)	[Mata (1998)]

Vaccine: *Vector/type:* Listeria monocytogenes *Strain:* HXB2 *HIV component:* Gag

- BALB/c mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways
- This is the immunodominant CTL epitope in Gag in BALB/c mice

- AMQMLKETI does not contain established Kd anchoring residue in position 2, tyrosine or phenylalanine, thus deviating from the typical Kd anchoring motif – the lack of the aromatic anchor residue is compensated for by interaction of the glutamine at P3 with pocket D of Kd

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p24(65–73) Gag(199–207 HXB2) AMQMLKETI Vaccine murine(H-2^d) [Qiu (1999)]

Vaccine: *Vector/type:* DNA *Strain:* HXB2 *HIV component:* gag

- Different expression vectors were tested to increase Gag expression in cell lines and create suitable vectors for DNA vaccines
- Stable Gag expression was achieved in murine p815 cells, using a Gag gene that had mutated silent base positions that disrupt inhibitory RNA sequences which promote RNA degradation
- Silent mutations were more effective than introduction of the D retrovirus cis-acting posttranscriptional control element (CTE) for enhancing Gag expression
- The gag vector with silent mutations given as a vaccine to BALB/c mice gave CTL responses in splenic mononuclear cells, using peptide pulsed cells as targets

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p24(65–73) p24(199–207 SF2) AMQMLKETI Vaccine murine(H-2^d) [Neidleman (2000)]

Vaccine: *Vector/type:* protein, vaccinia *Strain:* SF2 *HIV component:* soluble Gag, or GagPol expressing vaccinia *Stimulatory Agents:* heat-labile enterotoxin (LT) from E. coli

- Epitope name: p7g. Intranasal immunization of CB6F1 (H2bxd) mice with soluble gag p55 with LT ADP-ribosyltransferase mutants (LTK63 and LTK73) from Escherichia coli as adjuvants was tested
- Intranasal and intramucosal immunization of p55 gag protein with LTK63 or LTK72 adjuvant induced a CTL response comparable to intramuscular immunization responses
- Oral co-administration of LTR72, with residual ADP-ribosyltransferase activity, induced systemic CTL responses, but LTK63 with no ADP-ribosyltransferase activity did not

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p24(69–86) Gag(201–218 LAI) LKETINEEAAEWDRVP-V HIV-1 infection human( ) [Buseyne (1993a)]

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed cytotoxic activity against at least one HIV protein was detected in 70% of infected children
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures
- Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag

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p24(70–78) Gag(202–210 HXB2) KETINEEAA HIV-1 infection human(B*4002) [Mulligan (2001)]

- Epitope G20 from Patient 12129 with HLA genotypes A*0207, A*0217, B*0801, B*4002, Cw*0303, Cw*07(01, 06)

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p24(71–80) p24(203–212) ETINEEAAEW HIV-1 infection human(A*2501) [Klenerman (1996)]

- The epitope was defined through direct stimulation of PBMC with 20-mer peptides
- This epitope is in a conserved region and is found in most B, D, and E subtype isolates
- DTINEEAAEW is found in A and some D subtype sequences

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p24(71–80)	p24(203–212)	ETINEEAAEW	HIV-1 infection	human(A*2501)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*2501 epitope

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p24(71–80)	p24(203–212)	ETINEEAAEW	HIV-1 infection	human(A*2501)	[van Baalen (1996)]

- Conserved between B and D subtypes, variable in other clades; a consensus of clades A,C, F, G, and H and a peptide of HIV-2ROD over this region were not recognized by CTL recognizing the index peptide
- C. Brander notes that this is an A*2501 epitope in the 1999 database

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p24(71–80)	p24( )	ETINEEAAEW		human(A25)	[Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective
- HIV-2 sequence: EIINEEAAEW, no cross-reactivity [van Baalen (1996)]

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p24(71–80)	p24(203–212 SF2)	ETINEEAAEW	HIV-1 infection	human(A25)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A25+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/2 group 2, and 1/3 group 3

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p24(71–80)	p24(203–212)	DTINEEAAEW	HIV-1 exposed seronegative, HIV-1 infection	human(B53)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B53 women, 0/2 HEPS and 7/9 HIV-1-infected women recognized this epitope
- The dominant response to this HLA allele was to this epitope in 4 of the 7/9 responsive HIV-1-infected women

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p24(71–80)	p24(203–212 subtype A consensus)	DTINEEAAEW	HIV-1 infection	human(B53)	[Dorrell (2001)]

- In clade A infected Gambians, three HLA-B53 epitopes were defined in Gag p24 using ELISPOT, tetramer, and cytotoxicity assays

- Two of the new epitopes lacked the predicted by P2 anchors, DTINEEAAEW and QATQEVKNM, and bound to B53 with high affinity, thus extending the anchor residue motif for B53 and the related B35
- Two overlapping 20 mer peptides carry this complete epitope, but only one stimulates recognition, which could be due to different peptide processing
- DTINEEAAEW was recognized in only 2/7 HLA-B53 subjects
- DTINEEAAEW was not A subtype specific and there was cross-recognition although diminished, of the subtype B, C, and D variant, ETINEEAAEW
- In one of the two subjects there was cross-recognition of the HIV-2 version of the epitope, EIINEEAADW

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p24(71–90)	p24(203–222 SF2)	ETINEEAAEWDRVHP-VVHAGP	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA-A2, B21

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p24(78–86)	Gag(210–218 HXB2)	AEWDRVHPV	HIV-1 infection	human(B*4002)	[Mulligan (2001)]

- Epitope G21,G22 from Patient 07118 with HLA genotypes A*0209, A*3201, B*4002, B*5301, Cw*0202, Cw*0401
- Epitope G21,G22 Patient 07118 has 4 more optimal peptides P55, PIQKETWETW with HLA A*3201; N10, KEKGGLEGL with HLA B*4002; G31, QASQEVKNW with HLA B*5301;G43, TERQANFL with HLA B*4002

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p24(83–92)	p24(215–223 IIIB)	VHPVHAGPIA	HIV-1 infection	human(B55)	[Sipsas (1997)]

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB
- LHPVHAGPVA, a variant found in HIV-1 PH136, was also recognized
- LHPVHAGPIA, a variant found in HIV-1 RF, was also recognized
- LHPVHAGPIT, a variant found in HIV-1 MN, was also recognized
- LHPAQAGPIA, a variant found in HIV-1 JH3, was recognized at high peptide concentrations

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p24(87–101)	Gag(219–233 LAI)	HAGPIAPGQMREPRG	HIV-1 infection	human( )	[Buseyne (1993a)]

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed cytotoxic activity against at least one HIV protein was detected in 70% of infected children
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures
- Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag

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p24(87–101)	p24(219–233 BRU)	HAGPIAPGQMREPRG	HIV-1 infection	human(A2)	[Claverie (1988)]

- One of four epitopes predicted then shown to stimulate HLA-A2 restricted CTL line

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p24(91–110)	p24(223–242 SF2)	IAPGQMREPRGSDIAG-TTST	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein

- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA-A2, A24, B13, B35

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p24(101–120) p24(233–252 SF2) GSDIAGTTSTLQEQIG-WMTN HIV-1 infection human( ) [Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA-A26, A30, B38

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p24(107–114) Gag(239–247 SF2) TTSTLQEQI Vaccine murine(H-2K^d) [Mata (1998)]

Vaccine: *Vector/type:* Listeria monocytogenes *Strain:* HXB2 *HIV component:* Gag

- BALB/c mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways

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p24(108–117) ( ) TSTLQRQIGW HIV-1 infection human( ) [Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized in 1/22 HEPS sex worker controls (ML1250)

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p24(108–117) p24(240–249 LAI) TSTLQEQIGWF HIV-1 infection human(B*57,B*5801) [Goulder (1996b)]

- Response to this epitope was found in 4 slow progressing HLA-B*57 individuals, in 2 it was dominant or very strong
- For one donor (from Zimbabwe) this was defined as the optimal peptide
- This epitope can be presented in the context of the closely related HLA molecules B*5801 and B*57

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p24(108–117) p24(241–250 LAI) TSTVEEQQIW HIV-2 infection human(B*5801) [Brander & Goulder(2001)]

- C. Brander notes this is a B*5801 epitope

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p24(108–117) P24(240–249 LAI) TSTLQEQIGW HIV-1 infection human(B*5801) [Brander & Goulder(2001)]

- C. Brander notes this is a B*5801 epitope

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p24(108–117) p24(233–252) TSTLQEQIGW HIV-1 infection human(B57) [Bernard (1998)]

- This study focuses on six rare HIV-infected long-term survivors who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population

- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs
- Epitope sequences were deduced from larger reactive peptides based on HLA binding motifs – XSXXXXXXXW is a B57 binding motif, and CTL activity against TSTLQEQIGW has been found in two other B57 long-term non-progressors

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p24(108–117) Gag( ) TSTLQEQIGW HIV-1 infection human(B57) [Goulder (2001b)]

- Epitope name: TW10. Dominant epitope in acute infection in patient PI004, who did not receive any antiviral therapy
- 1-2 months post seroconversion, subject PI004 displayed a significant decrease in TW10 peptide recognition, followed by an increased CTL response against epitope SL9, SLYNTVATL and other epitopes
- Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond

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p24(108–117) p24(108–117) TSTLQEQIGW HIV-1 infection human(B57) [Oxenius (2000)]

- Epitope name: TST. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- None of the 8 study subjects recognized this epitope but none were HLA B57+

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p24(108–117) p24(108–117) TSTLQEQIGW HIV-1 infection human(B57) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p24(108–117) p24(235–243) TSTLQEQIGW HIV-1 exposed seronegative, HIV-1 infection human(B57,B58) [Kaul (2001a)]

- TSTLQEQIGW cross reacts with both for the A and B clades
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

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p24(108–117) p24(241–250) TSTVEEQQIW HIV-2 infection human(B58) [Bertoletti(1998)]

- HIV-2 epitope defined from an infection in Gambia, Bertoletti, Pers. Comm.
- All HIV-2 sequences from the database are TSTVEEQIQW in this region, not TSTVEEQQW as in the paper

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p24(108–117) p24( ) TSTLQEQIGW HIV-1 exposed seronegative human(B58) [Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective
- HIV-2 sequence: TSTVEEQIQW, CTL are cross-reactive, [Bertoletti (1998)]

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p24(108–117)	p24(240–249)	TSTLQEQIGW	HIV-2 infection	human(B58)	[Bertoletti (1998)]

- CTL responses in HLA-B*5801 positive HIV-2 infected individuals have a dominant response to Gag and tolerate extensive substitution, thus HLA-B*5801+ individuals may have an enhanced potential for cross-protection between HIV-1 and HIV-2
- This can be an immunodominant epitope in HLA-B57 and B*5801 infected individuals, and is associated with long-term non-progression [Goulder (1996b)]
- HIV-2 sequence: HIV-2 ROD has the epitope sequence TSTVEEQIQW, and the CTL from a person infected with HIV-2 was cross-reactive with HIV-1 epitopes
- The epitope is TSTLQEQIGW in HIV-1 B clade, and TSTVEEQIQW in HIV-2 ROD
- HLA B*5801 and B35 may preferentially select HIV-1 and HIV-2 cross-reactive epitopes

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p24(108–117)	p24(240–249 SF2)	TSTLQEQIGW	HIV-1 infection	human(B58)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B58+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 1/1 group 2, and 0/0 group 3

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p24(108–117)	p24(108–117)	TSTLQEQIGW	HIV-1 infection	human(B58)	[Goulder (2001d)]

- Epitope name: TW10. Responses to this dominant A3-restricted Gag epitope are present during the time of decreasing viral load in acute infection
- Mutations in this epitope were observed in autologous clones of subjects who were B58-positive with a higher frequency than those who were B58-negative (P = 0.02)
- These mutations are being sexually transmitted in adult infections

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p24(108–118)	p24(240–249 LAI)	TSTLQEQIGWF	HIV-1 infection	human(B*5701)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*5701 epitope

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p24(109–117)	Gag(241–249 LAI)	STLQEQIGW	HIV-1 infection	human(B*5701 B*5801)	[Klein (1998)]

- B57 has been associated with long-term non-progression in the Amsterdam cohort
- The most pronounced CTL responses in HLA B*5701 LTS were to RT and Gag

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p24(118–126)	Gag(282–290)	MTNNPPIPV	HIV-1 infection	human(A2 supertype)	[Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs

	• A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus • This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)				
p24(121–135)	p24(253–267)	NPPIPVGEIYKRWII	HIV-1 infection	human(B8)	[Gotch (1990)]
	• High frequency of memory and effector Gag-specific CTL				
p24(121–135)	p24(255–274 SF2)	NPPIPVGEIYKRWII	HIV-1 infection	human(B8)	[Goulder (1997a), Phillips (1991)]
	• Longitudinal study of CTL escape mutants in people with the appropriate HLA types – little variation was observed in the immunodominant B27 epitope, relative to B8 epitopes, which varied over time • [Goulder (1997a)] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA B27 patients				
p24(121–135)	p24(121–135)	NPPIPVGEIYKRWII	HIV-1 infection	human(B8)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
p24(121–140)	p24(253–272)	NPPIPVGEIYKRWIILG-LNK	HIV-1 infection	human( )	[Lieberman (1995)]
	• HIV-specific CTL lines developed by *ex vivo* stimulation with peptide				
p24(121–140)	p24(253–272 SF2)	NPPIPVGEIYKRWIILG-LNK	HIV-1 infection	human( )	[Lieberman (1997a)]
	• Of 25 patients, most had CTL specific for more than one HIV-1 protein • Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag • Two of these 12 had CTL response to this peptide • The responding subjects were HLA-A2, A3, B8, B62, and HLA-A1, B8, B18				
p24(121–140)	p24(253–272 SF2)	NPPIPGEIKRWIILGNIK	HIV-1 infection	human( )	[Lieberman (1997b)]
	• CTL expanded *ex vivo* were later infused into HIV-1 infected patients				
p24(121–140)	p24(255–274 SF2)	NPPIPVGEIYKRWIILG-LNK	HIV-1 infection	human( )	[van Baalen (1993)]
	• Gag CTL epitope precursor frequencies were estimated and peptide mapping was performed				
p24(121–142)	p24(253–274 BH10)	NPPIPVGEIYKRWIILG-LNKIV	HIV-1 infection	human(B8)	[Johnson (1991)]
	• Gag CTL response studied in three individuals				

p24(121–152)	Gag(183–214 LAI)	NPPIPVGEIYKRWIILG-LNKIVRMYSPTSILD	Vaccine	human( )	[Gahery-Segard (2000)]

Vaccine: *Vector/type:* lipopeptide *HIV component:* six peptides

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 9/10 reacted to this peptide
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in four vaccinees
- All of the 12 tested had an IgG response to this peptide

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p24(121–152)	Gag( )	NPPIPVGEIYKRWIILG-LNKIVRMYSPTSILD	HIV-1 infection, Vaccine	human(A*0201)	[Seth (2000)]

Vaccine: *Vector/type:* lipopeptide *HIV component:* gag peptide

- Immunization of 2/4 HIV seropositive HLA selected individuals with a 32 amino acid Gag lipopeptide that contains CTL epitopes restricted by HLA A33, B8, B27, B35, and Bw62 gave a transient increase in peptide-specific bulk CTL response, but they did not decrease plasma viral
- Placebo and HLA mis-matched controls showed no change in CTL
- The responders carried HLA Bw62 and B35 – the two that did not respond carried B35 and B8

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p24(122–130)	p24( )	PPIPVGDIH	HIV-1 infection	human( )	[Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized in 1/22 HEPS sex worker controls, ML887

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p24(122–130)	p24(260–268 LAI)	PPIPVGDIY	HIV-1 or HIV-2 infection	human(B*3501)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*3501 epitope

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p24(122–130)	p24(245–253 HIV-2)	NPVPVGNIY	HIV-1 infection	human(B*3501)	[Rowland-Jones (1995)]

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p24(122–130)	p24(245–253 HIV-2)	NPVPVGNIY	HIV-1 infection	human(B*3501)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*3501 epitope

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p24(122–130)	p24(260–268 LAI)	PPIPVGDIY	HIV-1 or HIV-2 infection	human(B35)	[Rowland-Jones (1995)]

- Defined as minimal peptide by titration curve, PPIPVGEIY and HIV-2 form NPVPVGNIY are also recognized

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p24(122–130)	p24(260–268 LAI)	PPIPVGDIY	*in vitro* stimulation	human(B35)	[Lalvani (1997)]

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors

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p24(122–130)	p24(260–268 LAI)	PPIPVGDIY	HIV-1 infection	human(B35)	[McMichael & Walker(1994)]

- Review of HIV CTL epitopes

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p24(122–130)	p24( )	PPIPVGEIY	HIV-1 exposed seronegative	human(B35)	[Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among B and D clade viruses
- The clade A version of the epitope, PPIPVGDIY, was preferentially recognized by CTL

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p24(122–130)	( )	PPIPVGEIY	HIV-1 infection	human(B35)	[Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

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p24(122–130)	p24( )	PPIPVGDIY		human(B35)	[Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective

- HIV-2 version of this epitope is not conserved: NPVPVGNIY, but the CTLs are cross-reactive – one of five B35 CTL epitopes that are cross-reactive, see also [Rowland-Jones (1995)]

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p24(122–130) p24(260–268) PPIPVGDIY HIV-1 infection human(B35) [Oxenius (2000)]

- Epitope name: PPI. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- One of two HLA B35+ among the eight study subjects recognized this epitope
- Patient SC15 (HLA A1/68, B8/35, Bw4/6, Cw4/0704) was given acute and sustained therapy and recognized epitopes PPIPVGDIY and VPLRPMTY during 331 days of HAART treatment

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p24(122–130) p24(122–130) PPIPVGDIY HIV-1 infection human(B35) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p24(122–130) p24(254–262 SF2) PPIPVGDIY HIV-1 infection human(B35) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 0/2 group 2, and 1/1 group 3

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p24(122–130) p24(260–268) PPIPVGDIY HIV-1 exposed seronegative, HIV-1 infection human(B35) [Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B35 women, 1/3 HEPS and 3/4 HIV-1-infected women recognized this epitope
- The dominant response to this HLA allele was to this epitope in the 1/3 HEPS cases and in all the 3/4 responsive HIV-1-infected women
- Subject ML 857 shifted from an A*6802 DTVLEDINL and B35 H/NPDIVIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion

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p24(124–138)	p24(256–270 LAI)	IPVGEIYKRWIILGL	HIV-1 infection	human(B8)	[Buseyne (1993b)]
• Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people					
p24(124–138)	Gag(256–270 LAI)	IPVEGEIYKRWIILGL	HIV-1 infection	human(B8)	[Buseyne (1993a)]
• Vertical transmission of HIV ranges from 13% to 39%					
• Primary assays showed cytotoxic activity against at least one HIV protein was detected in 70% of infected children					
• Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures					
• Two children, EM16 (CDC P2A+D2) and EM18 (CDC P2A), had a CTL response to this epitope, and it was shown to be presented by B8 in EM18					
p24(127–135)	p24(259–267 SF2)	GDIYKRWII	HIV-1 infection	human(B*0801)	[McAdam (1998)]
• GDIYKRWII specific CTL clone also recognized GEIYKRWII					
p24(127–135)	p24(261–269)	GEIYKRWII	HIV-1 infection	human(B8)	[Sutton (1993)]
• Predicted epitope based on B8-binding motifs, from larger peptide NPPIPVGEIYKRWII					
p24(127–135)	p24(259–267)	GEIYKRWII	*in vitro* stimulation	human(B8)	[Zarling (1999)]
• This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses					
• Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA					
• A weak response to KLTPLCVSL was stimulated using macrophages as the APC					
• No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL					
p24(127–135)	p24(259–267 LAI)	GEIYKRWII	HIV-1 infection	human(B8)	[Klenerman (1994)]
• Naturally-occurring variant GDIYKRWII may act as antagonist					
p24(127–135)	p24(259–267)	GEIYKRWII	HIV-1 infection	human(B8)	[Betts (2000)]
• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant					
• Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes					
• 1/11 of the HLA A2+ was HLA A*0201, A31, B8, B51 and responded to this epitope as well as seven others					
p24(127–135)	p24(259–267)	GEIYKRWII	HIV-1 infection	human(B8)	[Nowak (1995)]
• Longitudinal study of CTL response and study of immune escape – GDIYKRWII could also stimulate CTL, reactivity fluctuated					
p24(127–135)	p24(259–267)	GEIYKRWII	HIV-1 infection	human(B8)	[McAdam (1995)]
• Equivalent sequence GDIYKRWII also recognized by CTL from some donors					

p24(127–135) p24(259–267) GEIYKRWII HIV-1 infection human(B8) [Oxenius (2000)]

- Epitope name: GEI. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- Six of the 7/8 study subjects that were HLA B8 recognized this epitope
- Patient SC2 (HLA A1, B7/8, Cw0701/0702, DR4/53, DQ7) had CTL responses against epitopes FLKEKGGL, GPKVKQWPL, and GEIYKRWII – FLKEKGGL tetramer staining steadily declined and at day 1340 the FLKEKGGL stained cells were no longer detected and the escape mutant FLKENGGI was found in 8/10 clones
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDLWIYHTQGYFPDWQNY, and GEIYKRWII and all responses declined during therapy initiated at day 390 but were restored when therapy became intermittent
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197
- Patient SC10(HLA A1/3, B8/35, DR1/8, DQ 4/5) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL and a response to GEIYKRWII through day 1088
- Patient SC12(HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKKKYKLK – GEIYKRWII and GGKKKYKLK responses were stimulated by a brief period off therapy
- Patient SC11(HLA A1, B8, Cw0201, DR3/11, DR52, DQ2/7) started therapy early, remained on therapy for 40 days, then reinitiated HAART at day 640, and had a CTL response to FLKEKGGL, GPKVKQWPL, and GEIYKRWII throughout and received a benefit from the early limited course therapy

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p24(127–135) p24(259–267 SF2) GEIYKRWII HIV-1 infection human(B8) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 2/3 group 1, 2/3 group 2, and 2/2 group 3

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p24(127–136) Gag(259–268 HXB2) GEIYKRWIIL HIV-1 infection human(B*0801) [Mulligan (2001)]

- Epitope G26 from Patient 07111 with HLA genotypes A*0101, A*0301, B*0801, B*5802, Cw*0602, Cw*07(01, 06)

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p24(128–135) p24(260–267 LAI) EIYKRWII human(B*0801) [Brander & Goulder(2001)]

- C. Brander notes this is a B*0801 epitope

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p24(128–135)	p24(260–267 LAI)	EIYKRWII		human(B8)	[Goulder (1997g)]
• Defined in a study of the B8 binding motif					
p24(128–135)	p24( )	EIYKRWII	HIV-1 infection	human(B8)	[Goulder (2000a)]
• The CTL-dominant response was focused on this epitope in an HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study • Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses • Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa					
p24(128–135)	p24( )	DIYKRWII	HIV-1 infection	human(B8)	[Goulder (2000a)]
• The CTL-dominant response was focused on this epitope in an HIV+ South African – this epitope did not fall within the five most recognized peptides in the study • Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses • Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa					
p24(128–135)	p24( )	EIYKRWII	HIV-1 infection	human(B8)	[Goulder (2001b)]
• Epitope name: EI8. This peptide elicited a weak CTL response during acute HIV-1 infection in patient PI004 • Three CTL responses to epitopes, TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond					
p24(128–135)	p24( )	EIYKRWII	HIV-1 infection	human(B8)	[Kostense (2001)]
• HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load • Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional • In 15 of the patients, the proportion of IFNγ producing tetramer cells correlated with AIDS-free survival • 4/13 patients that reacted with EIYKRWII displayed epitope mutations in a minority of sequences, which did not seem to influence disease progression or viral load – these mutations were: Patient 156 (KIYKRWMI), Patient 36 (EIYKRRII), Patient 656 (KIYKRWII, EIYERWMI), and Patient 159 (EIYKRWVI) • Stimulation with HLA-B8 p24 and Nef epitopes significantly increased Nef-specific T-cell numbers in 2 patients (748 and 1113) • There were more functional IFN-γ producing Nef-specific T-cells within the T-cell population than there were active p24 Gag-specific T-cells					

p24(128–135)	p24(259–267)	DIYKRWII	HIV-1 infection	human(B8)	[Appay (2000)]

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV
- HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

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p24(128–135)	p24(128–135)	EIYKRWII	HIV-1 infection	human(B8)	[Day (2001)]

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual

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p24(128–135)	Gag( )	EIYKRWII	HIV-1 infection	human(B8)	[Goulder (2000b)]

- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA])
- HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection

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p24(129–136)	p24(263–270 SF2)	IYKRWIIL	HIV-1 infection	human(A*2402)	[Ikeda-Moore (1997)]

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402
- This peptide induced CTL in 1/4 HIV-1+ people tested
- IYKRWIIL bound to A*2402 with medium strength, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained

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p24(129–138)	p24(263–272 SF2)	IYKRWIILGL	HIV-1 infection	human(A*2402)	[Ikeda-Moore (1997)]

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402
- This peptide induced CTL in 1/4 HIV-1+ people tested
- IYKRWIILGL bound to A*2402 with medium strength, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained

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p24(129–138)	p24(263–272)	IYKRWIILGL	HIV-1 infection	human(B27)	[Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- 1/11 of the A2+ individuals was B27 and responded to IYKRWIILGL

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p24(130–148)	p24(265–280 BRU)	YKRWIILGLNKIVRMY-SPT	HIV-1 infection	human(B27)	[Dadaglio (1991)]

- Used as a positive control for HLA specificity

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p24(131–139)	p24(263–272)	KRWIILGNK	HIV-1 infection	human(B27)	[Durali (1998)]

- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env
- One of the patients was shown to react to this epitope: KRWIILGNK

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p24(131–139)	Gag(265–273)	KRWIILGLN	HIV-1 infection	chimpanzee(Patr-B*03)	[Balla-Jhagjhoorsingh (1999b)]

- Certain HLA-alleles have been associated with long-term survival – among them are HLA-B*27 and HLA-B*57
- Of more than 150 chimpanzees that have been reported to be infected with HIV-1, only one has developed AIDS
- CTL responses were studied in two HIV-1 infected chimpanzees that have strong CTL responses, and they responded to highly conserved epitopes that are recognized in humans in the context of HLA-B*27 and HLA-B*57
- The human HLA protein which presents this Patr-B*03 epitope is HLA B*2705, but the amino acid sequences in the binding pockets of HLA-B*2705 and Patr-B*03 are distinctive

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p24(131–140)	Gag(263–272 LAI)	KRWILLGLNK	HIV-1 infection	human( )	[Buseyne (1993a)]

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed cytotoxic activity against at least one HIV protein was detected in 70% of infected children
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures
- Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag

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p24(131–140)	p24(263–272)	KRWIILLGLNK	HIV-1 infection	human(B*27)	[Huang (2000)]

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed
- Increases in γ interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-γ-production ELISPOT
- In 3/3 HLA A*02, B*27 individuals, the dominant response in gag measured by both γ IFN production and T-cell lysis was to the B27 epitope, KRWIILLGLNK, not the A2 SLYNTVATL epitope

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p24(131–140)	p24(263–272 SF2)	KRWIILGLNK	HIV-1 infection	human(B*27)	[McAdam (1998)]

- Epitope invariant across clades A, B, C, and D

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p24(131–140)	p24(260–269 HIV-2)	RRWIQLGLQK		human(B*2703)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*2703 epitope

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p24(131–140)	p24( )	KRWIILGGLNK	HIV-1 infection	human(B*2705)	[Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- Tetramers with peptide variants KRWIILGGLNK and KRWIIMGGLNK were used – CTL from most B27 donors recognize both variants, although one of the three subjects recognized only KRWIILGGLNK
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

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p24(131–140)	p24(263–272 LAI)	KRWIILGLNK	HIV-1 infection	human(B*2705)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*2705 epitope

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p24(131–140)	p24(263–272)	KRWIILGLNK	HIV-1 infection	human(B*2705)	[Kelleher (2001)]

- A mutation in 4/5 B*2705 patients had substitution to lysine (K) at HIV-1 gag residue 264 (R264K), in three the change occurred late in infection – in one patient a substitution of glycine at HIV-1 gag residue 264 (R264G) was detected – these substitutions reduce binding to B27
- The R264K mutations were associated with an L268M mutation that may be compensatory, and R264G occurred in conjunction with E260D
- Positions 260, 264, and 268 all lie along one aspect of helix seven of the capsid protein, a region that is important for capsid self-association and assembly
- R264G and R264K escape mutation outgrowth occurred in conjunction with high viral loads

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p24(131–140)	p24(263–272)	KRWIIMGLNK	HIV-1 infection	human(B*2705)	[Appay (2000)]

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV
- HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

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p24(131–140)	p24(263–272 LAI)	KRWIILGLNK	HIV-1 infection	human(B*2705,B27)	[Goulder (1997c), Goulder (1997a)]

- HLA-B*2705 is associated with slow HIV disease progression
- 11/11 HLA-B*2705 donors make a response to this epitope, usually an immunodominant response
- This is a highly conserved epitope
- The HLA-B*2705 binding motif includes R at position 2, and L in the C-term position
- [Goulder (1997a)] is a review on CTL immune escape that discusses this epitope in the context of the difficulty in detection of immune escape – KRWIILGLNK and an R2K change, KKWIILGLNK, show little difference in titration curves, yet the K2 variants fail to bind to targets for more than 1 hour, while the R2 form can sensitize lysis by CTL for over 24 hours – minigene transfection experiments confirmed the importance of this for the CTL response

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p24(131–140) p24(260–269 HIV-2) RRWIQLGLQK human(B*2703) [Brander & Walker(1996)]

- HIV-2, HLA-B*2703, S. Rowland-Jones, Pers. Comm.

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p24(131–140) p24(263–272 LAI) KRWIILGLNK HIV-1 infection human(B27) [Fan (1997)]

- The capacity of dendritic cells to process and present antigen and stimulate anti-HIV-1 CTL memory responses was studied

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p24(131–140) Gag(263–272) KRWIILGLNK HIV-1 infection human(B27) [Zheng (1999)]

- Protein delivery (gp160 LAV, p66 LAV, and p24 NY5) to human dendritic cells (DC) with liposomes provides enhanced memory CTL response relative to delivery of protein alone
- Chloroquine administration enhanced epitope presentation, and brefeldin A and peptide aldehyde inhibitors inhibited antigen presentation, suggesting epitopes were processed by a classical proteasome pathway
- The CTL response to p24 was measured in individuals with a response to B27-KRWIILGLNK

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p24(131–140) p24(263–272 LAI) KRWIILGLNK HIV-1 infection human(B27) [Wilson (1998a)]

- HIV+ individuals were followed longitudinally using MHC tetramers in combination with 14 anti-BV chain MAbs, and clonal expansion of HIV-specific T-cells was followed *in vivo*
- Seven HIV+ people were studied, and all showed expansions of particular TCR BV clones, often several, relative to uninfected controls
- Three patients were followed in detail, TCR VB expansions persisted for 2 to 3 years, with occasional transient increases

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p24(131–140) p24( ) KRWIILGLNK HIV-1 infection human(B27) [Rowland-Jones (1997)]

- Described in this review as the first identified HIV CTL epitope

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p24(131–140) p24(263–272 LAI) KRWIILGLNK HIV-1 infection human(B27) [Buseyne (1993b)]

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people

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p24(131–140) p24(263–272 LAI) KRWIILGLNK HIV-1 infection human(B27) [McMichael & Walker(1994)]

- Review of HIV CTL epitopes

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p24(131–140)	p24(263–272)	KRWIIMGLNK	HIV-1 infection	human(B27)	[Klenerman (1994), Klenerman (1995)]

- Naturally-occurring variant KRWIILGLNK may act as antagonist

p24(131–140)	p24(265–274)	KRWIILGLNK	HIV-1 infection	human(B27)	[Moss (1995)]

- In one individual, TCR usage changed over time indicating that new populations of CTL can be recruited
- TCR usage showed a CTL clonal response to this epitope that persisted over 5 years
- CTL clones specific for HIV epitopes may represent between 0.2 and 1% of the total CD8+ population of T-cells

p24(131–140)	p24(265–276)	KRWIILGLNK		human(B27)	[Carreno (1992)]

- Included in HLA-B27 binding peptide competition study

p24(131–140)	p24(265–274 SF2)	KRWIILGLNK	HIV-1 infection	human(B27)	[Goulder (1997a), Phillips (1991)]

- Longitudinal study of CTL escape mutants – little variation was observed in the immunodominant B27 epitope, relative to B8 epitope
- [Goulder (1997a)] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA B27 patients

p24(131–140)	p24(263–272)	KRWIILGLNK	HIV-1 infection	human(B27)	[Goulder (1997a), Nietfeld (1995)]

- Single point mutations were introduced and viral viability and CTL recognition tested – an Arg to Lys change at anchor position P2 abrogates binding to B27, but doesn't change viral viability *in vitro*
- [Goulder (1997a)] is a review of immune escape that summarizes this study

p24(131–140)	p24(263–272)	KRWIIMGNK	HIV-1 infection	human(B27)	[Nowak (1995)]

- Longitudinal study of CTL response and immune escape – the form KRWIILGNK was also found, and both forms stimulate CTL

p24(131–140)	p24(263–272)	KRWIIMGLNK	HIV-1 infection	human(B27)	[Goulder (1997f), Goulder (1997a)]

- Six HLA-B27 donors studied make a strong response to this epitope
- In 4/6 cases, this was the immunodominant or only CTL response
- Two of the cases had an epitope switch to the form KKWIIMGLNK during a period of rapid decline to AIDS, following their asymptomatic period
- The arginine to lysine switch is in an anchor residue, and results in immune escape due to severely diminished binding to the B27 molecule
- [Goulder (1997a)] is a review of immune escape that summarizes this study in the context of CTL escape to fixation

p24(131–140)	p24( )	KRWIILGLNK		human(B27)	[Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5

- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective
- HIV-2 sequence: RRWIQLGLQK – this B27 epitope was not HIV-1 and HIV-2 cross-reactive

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p24(131–140) Gag( ) KRWILGLNK computer prediction (B27) [Schafer (1998)]

- This study uses EpiMatrix for T-cell epitope prediction to identify possible HLA-B27 and A-2 CTL epitopes in HIV
- Based on EpiMatrix predictions, 28 peptides were synthesized and tested using T2 binding assays for potential HLA A2 or B27 binding, and 12 of these were shown to bind to the predicted HLA molecule
- Two of these 12 peptides had been previously identified as CTL epitopes: HLA-B27 KRWILGLNK and HLA-A2 ILKEPVHGV
- This peptide sequence is not conserved between clades, but is found in most B clade isolates

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p24(131–140) p24(263–282) KRWIILGLNK HIV-1 infection human(B27) [Bernard (1998)]

- This study focuses on six HIV-infected long-term survivors who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs
- Epitope sequences were deduced from larger reactive peptides based on HLA binding motifs within the peptide – XRXXXXXXXK is a B*2705 binding motif

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p24(131–140) p24(265–274 SF2) KRWIILGLNK HIV-1 infection human(B27) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B27+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/1 group 3

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p24(131–140) p24(263–272) KRWIILGLNK HIV-1 exposed seronegative, HIV-1 infection human(B27) [Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Subject ML 1760 had an A2 response to ILK[D/E]PVHGV prior to seroconversion, and gained responses to epitopes A2 SL[F/Y]NTVATL and B27 KRWII[L/M]GLNK post-seroconversion

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p24(131–140)	p24(131–140)	KRWIILGLNK	HIV-1 infection	human(B27)	[Day (2001)]
p24(131–140)	p24(260–299)	RRWIQLGLQK	HIV-1 infection	human(B27)	[Day (2001)]
p24(131–140)	p24(131–140)	KRWIILGLNK	HIV-1 infection	human(B27)	[Goulder (2001c)]

- Epitope name: KK10. 85% of B27+ adults have CTL that recognize this epitope, but only 2/6 children did
- Responses to this dominant B27-restricted Gag epitope are present during the time of decreasing viral load in acute infection
- Three children who shared B27 with their mothers did not respond to this epitope and inherited escape mutations from their mothers
- A transmitted R132T anchor residue mutation abrogated binding to B27
- In the three children infected with the non-binding KK10 variants, the dominant CTL specificity was still HLA-B27-restricted, but it was directed against an epitope in p17, IRLRPGGKK, only rarely recognized in adults when KRWIILGLNK is the dominant response
- Mutations in this epitope were observed in autologous clones of subjects who were B27-positive with a higher frequency than those who were B27-negative (P = 0.0005)
- These mutations are being sexually transmitted in adult infections

p24(131–142)	p24(265–276)	KRWIILGLNKIV	Peptide-HLA interaction	human(B27)	[Jardetzky (1991)]

- Epitope examined in the context of peptide binding to HLA-B27

p24(131–142)	p24(263–274 LAI)	KRWIILGLNKIV	HIV-1 infection	human(B27)	[Fan (1997)]

- The capacity of dendritic cells to process and present antigen and stimulate anti-HIV-1 CTL memory responses was studied

p24(131–142)	p24(131–142)	KRWIILGLNKIV	HIV-1 infection	human(B27)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

p24(131–145)	p24( )	KRWILGLNKIVRMY	HIV-1 infection	human( )	[Goulder (2000a)]

- The CTL-dominant response was focused on this epitope in an HIV+ African American living in Boston with unknown HLA – this epitope did not fall within the three most recognized peptides in the study
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

p24(131–145)	p24(263–277 LAI)	KRWIILGLNKIVMRY	HIV-1 infection	human(A33)	[Buseyne (1993b)]

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people

p24(131–145)	p24(266–277)	KRWIILGLNKIVRMY	Vaccine	human(B27)	[Nixon (1988)]

Vaccine: *Vector/type:* vaccinia *HIV component:* Gag

	• Gag CTL epitope mapped with rec gag-vaccinia and synthetic peptides • This was the first HIV-1 epitope to be mapped				
p24(131–145)	p24(266–277 LAI)	KRWIILGLNKIVMRY	HIV-1 infection	human(B27)	[Meyerhans (1991)]
	• Longitudinal study showing persistence of epitope despite CTL activity				
p24(131–145)	p24(265–279)	KRWIILGLNKIVRMY	HIV-1 infection	human(B27)	[Nixon (1990), Rowland-Jones (1999)]
	• HIV-1 and HIV-2 cross-reactive CTL clone, highly conserved epitope • Reviewed in Rowland-Jones99, notes that it did not appear cross-reactive with HIV-2 in Rowland-Jones98, HIV-2 form: RRWIQL-GLQK				
p24(131–146)	p24(265–279)	KRWIILGLNKIVRMYC	HIV-1 infection	human(B27)	[Bouillot (1989)]
	• HLA-B27 restricted epitope also binds to HLA-A2 and HLA-B37 in solid phase assay				
p24(131–150)	p24(263–282 SF2)	KRWIILGLNKIVRMYS-PTSI	HIV-1 infection	human( )	[Lieberman (1997a)]
	• Of 25 patients, most had CTL specific for more than one HIV-1 protein • Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag • One of these 12 A-2 had CTL response to this peptide • The responding subject was HLA-A3, A32, B51, B62				
p24(131–150)	p24(265–284 SF2)	KRWIILGLNKIVRMYS-PTSI	HIV-1 infection	human(Bw62?)	[van Baalen (1993)]
	• Gag CTL epitope precursor frequencies estimated				
p24(131–152)	p24(263–284 BH10)	KRWIILGLNKIVRMYS-PTSILD	HIV-1 infection	human(Bw62)	[Johnson (1991)]
	• Gag CTL response studied in three individuals				
p24(132–145)	Gag( )	KWILGLNKIVRMY	HIV-1 infection	human( )	[Weekes (1999a)]
	• Peptide 728: Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28- CD8+ CTLp populations				
p24(132–145)	Gag( )	KWILGLNKIVRMY	HIV-1 infection	human(B27)	[Weekes (1999b)]
	• Peptide 728: Almost all CD8+ T-cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed the CD28 depleted cell population • HIV CTL responses to 3 Env and 2 Gag peptides were studied • The clonal composition of TCR Vβ responses were studied and was found to be highly focused, with one TCR β-chain sequence tending to dominate the peptide-specific response – clones to this epitope were Vβ22.1				

p24(134–143)	p24( )	IILGLNKIVR	HIV-1 exposed seronegative	human(A33)	[Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among A, B and D clade viruses

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p24(136–145)	p24(268–277 LAI)	LGLNKIVRMY	HIV-1 infection	human(Bw62)	[McMichael & Walker(1994)]

- Predicted from larger peptide
- Review of HIV CTL epitopes
- Also P. Johnson, Pers. Comm.

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p24(136–146)	p24(271–281)	LGLNKIVRMYS	HIV-1 infection	human(B62)	[Lubaki (1997)]

- Eighty-two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response
- A subject who was B62+ had CTL that recognized this epitope, and p17 KIRLRPGGKKKYKL, and one additional unknown epitope
- The two clones that recognized this epitope used two different Vβ genes, further demonstrating a polyclonal response

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p24(136–146)	p24(136–146)	LGLNKIVRMYS	HIV-1 infection	human(B62)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p24(137–145)	p24( )	GLNKIVRMY	HIV-1 infection	human( )	[Goulder (2000a)]

- The CTL-dominant response was focused on this epitope in an HIV+ South African living in Durban, HLA A2/- B5802/62 Cw4/6 – this epitope did not fall within the three most recognized peptides in the study
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
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p24(137–145)	p24(272–280 LAI)	GLNKIVRMY	HIV-1 infection	human(B*1501)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*1501 epitope

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p24(137–145)	p24(272–280 LAI)	GLNKIVRMY	HIV-1 infection	human(B62)	[Goulder (1997a)]

- This paper is a review of CTL and immune evasion, but it presents a study of a shift from an HLA-A*0201 response to SLYNTVATL, to a B62 response to GLNKIVRMY

- As long as a strong CTL response to SLYNTVATL was evident, the epitope variants SLFNTVATL or SLYNTIATL dominated the viral population – eventually the CTL response to the index peptide became undetectable, the CTL response shifted to a focus on GLNKIVRMY, and the index peptide SLYNTVATL once again established itself as the dominant form

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p24(137–145)	p24( )	GLNKIVRMY	HIV-1 infection	human(B62)	[Goulder (2000a)]

- The CTL-dominant response was focused on this epitope in an HIV+ African American living in Boston – this epitope did not fall within the three most recognized peptides in the study
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

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p24(137–145)	p24(267–277 SF2)	GLNKIVRMY	HIV-1 infection	human(B62)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B62+ individuals that had a CTL response to this epitope broken down by group: 0/1 group 1, 0/1 group 2, and 1/1 group 3

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p24(137–145)	p24(137–145)	GLNKIVRMY	HIV-1 infection	human(B62)	[Day (2001)]

- No immunodominant responses were detected to four B62-restricted epitopes tested

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p24(143–150)	p24(273–283 IIIB)	RMYSPTSI	HIV-1 infection	human(B*5201)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*5201 epitope

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p24(143–150)	p24(273–283 IIIB)	RMYSPTSI	HIV-1 infection	human(B52)	[Brander (1999)]

- Epitope name: SL9. Multiple natural variations in the SL9 flanking regions of the immunodominant epitope SLYNTVATL were tested and found not to adversely affect CTL recognition or prevent epitope processing, suggesting that viral escape from the HLA-A*0201-restricted CTL response against SLYNTVATL is probably not linked to variations in the flanking regions of this epitope
- The CTL response to RMYSPTSI was used as a control

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p24(143–150)	p24(273–283 IIIB)	RMYSPTSI	HIV-1 infection	human(B52)	[Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- No variants of this epitope were found in a non-transmitting mother that had a CTL response to this epitope

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p24(143–150)	p24(143–150)	RMYSPTSI	HIV-1 infection	human(B52)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

p24(151–170)	p24(283–302 SF2)	LDIRQGPKEPFRDYVD-RFYK	HIV-1 infection	human( )	[McAdam (1998)]

p24(155–177)	p24(287–309)	QGPKEPFRDYVDRFY-KTLRAEQA?	Vaccine	murine( )	[Nakamura (1997)]

Vaccine: *Vector/type:* peptide *HIV component:* p24

- Mice immunized with this synthetic peptide generated specific CTLs, a proliferative response, and antibodies
- The CTL epitope was shown to be located in positions 291-300

p24(157–178)	p24(290–309)	PKEPFRDYVDRFYKTL-RAEQAS	HIV-1 infection	human(B14)	[Musey (1997)]

- Cervical and peripheral blood derived CTL clones from an HIV-infected woman recognized this epitope

p24(159–168)	Gag(291–300)	EPFRDYVDRF	Vaccine	murine(H-2^d)	[Billaut-Mulot (2001)]

Vaccine: *Vector/type:* DNA with DNA boost, DNA with recombinant protein boost *Strain:* LAI *HIV component:* Gag, Tat, Nef *Stimulatory Agents:* IL-18

- DNA vaccinated BALB/c mice primed and boosted with the multiepitopic vaccine with IL-18 showed lymphoproliferative responses 7 weeks post immunization
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime/DNA boost was more effective than DNA prime protein boost
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine induced HIV-1 specific Th1 cytokines (IL-2 and IFN-γ)
- Co-administration of IL-18 increased T-cell responses but decreased anti-HIV antibody levels

p24(159–178)	Gag( )	EPFRDYVDRFFKTLRA-EQAT		human(B*44031)	[Novitsky (2001)]

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort
- 16/46 (34.8%) had CTL responses to one or more peptides within the second immunodominant region of Gag (peptides SILDIKQGP-KEPFRDYVDRF, EPFRDYVDRFFKTLRAEQAT, and FKTLRAEQATQEVKNWMTDT) with ELISPOT results median and range 500 (100 to 1,250) SFC/10^6 PBMC
- 3/6 (50%) carriers of HLA-B*44031 showed CTL responses to the peptide EPFRDYVDRFFKTLRAEQAT

p24(161–170)	( )	FRDYVDRFFK	HIV-1 infection	human( )	[Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized in 1/22 HEPS sex worker controls, ML1732

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p24(161–170)	p24( )	FRDYVDRFYK	HIV-1 infection	human(B*1801)	[Ogg (1998a)]

- Noted in Brander 1999, this database, to be B*1801, FRDYVDRFY

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p24(161–170)	p24( )	FRDYVDRFYK	HIV-1 infection	human(B*1801)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*1801 epitope

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p24(161–170)	p24(161–170)	FRDYVDRFYK	HIV-1 infection	human(B18)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p24(161–170)	p24(293–302)	FRDYVDRFYK	HIV-1 exposed seronegative, HIV-1 infection	human(B18)	[Kaul (2001a)]

- Variants FRDYVDRF(Y/F)K are specific for the B,D/A,C clades
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B18 women, 3/4 HEPS and 1/9 HIV-1-infected women recognized this epitope, likelihood ratio 5.3, p value 0.04, and HEPS women tended to respond to FRDYVDRFY/FK, while infected women tended to respond to YPLTFGWCY/F
- The dominant response to this HLA allele was to this epitope for all 3/4 HEPS cases and for the single HIV-1 infected woman that responded to this epitope
- Four epitopes were considered to be “resistant epitopes”, as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILKD/EPVHGV in RT, A*6802 DTVLEDINL in Protease, B14 DLNM/TLNI/VV in p24 and B18 FRDYVDRFY/FK also in p24
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort

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p24(161–180)	p24(293–312 SF2)	FRDYVDRFYKTLRAE-QASQD	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA-A2, A3, B8, B62

p24(161–180)	p24(293–312 SF2)	FRDYVDRFYKTLRAE-QASQD	HIV-1 infection	human( )	[Lieberman (1997b)]

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients

p24(161–180)	p24(293–312 SF2)	FRDYVDRFYKTLRAE-QASQD	HIV-1 infection	human(B71)	[McAdam (1998)]

p24(162–171)	p24(296–306)	RDYVDRFFKTL	HIV-1 exposed seronegative, HIV-1 infection	human(A24)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-A24 women, 0/4 HEPS and 6/10 HIV-1-infected women recognized this epitope, likelihood ratio 7.2, p value 0.03, and (R)YL(R/K)DQQLL tended to be reactive in HEPS and infected women, RDYVDRFFKTL in infected women only
- The dominant response to this HLA allele was to this epitope in all of the 6/10 HIV-1-infected women
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort
- Subject ML 1707 started with a CTL response to A*6802 DTVLEDINL prior to seroconversion, and switched to A*6802 ETAYFILKL and A24 RDYVDRFFKTL post-seroconversion

p24(162–172)	p24(296–306 clade A)	RDYVDRFFKTL	HIV-1 infection	human(A*2402)	[Dorrell (1999)]

- CTL responses in three individuals with non-clade B infections were studied, two with subtype A infections, one with subtype C – their infections all originated in East Africa
- This epitope is similar to the A24 DYVDRYFKT epitope found for B subtype, but CTL from this A subtype infection required the additional Arg – the B clade sequence change from F to Y diminished CTL reactivity
- C. Brander notes that this is an A*2402 epitope in the 1999 database

p24(162–172)	p24(296–306 clade A)	RDYVDRFFKTL	HIV-1 infection	human(A*2402)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*2402 epitope

p24(162–172)	p24(293–312 LAI)	RDYVDRFYKTL	HIV-1 infection	human(B*4402)	[Brander & Goulder(2001)]
	• C. Brander notes this is a B*4402 epitope				
p24(162–172)	p24(162–172)	RDYVDRFYKTL	HIV-1 infection	human(B44)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
p24(162–172)	p24(162–172)	RDYVDRFYKTL	HIV-1 infection	human(B44)	[Day (2001)]
p24(162–172)	p24(293–312 LAI)	RDYVDRFYKTL	HIV-1 infection	human(B44, A26 or B70)	[Ogg (1998a)]
p24(163–172)	p24(163–172)	DYVDRFYKTL	HIV-1 infection	human(A24)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
p24(164–172)	p24(298–306 clade A)	YVDRFFKTL	HIV-1 infection	human(A26 or B70)	[Dorrell (1999)]
	• CTL responses in three individuals with non-clade B infections were studied, two with subtype A infections, one with subtype C – their infections all originated in East Africa • This CTL epitope is conserved in A and C subtype, and B clade sequences tend to have a change from F to Y, YVDRFYKTL – both variants showed strong CTL reactivity • CTL reacted with targets presenting either in the context A26 or B70 – the epitope has the HLA-26 motif of Val at position 2 and Leu at the carboxy terminus, and the B70 anchor residue motif is unknown				
p24(164–172)	Gag(298–306 subtype A)	YVDRFFKTL	HIV-1 infection, *in vitro* stimulation	human(A26 or B70)	[Dorrell (2001)]
	• In vitro restimulation of CTL specific for dominant epitopes from infected individuals is possible using recombinant modified vaccinia virus Ankara (MVA) carrying A or D subtype HIV-1 Gag proteins				
p24(164–172)	Gag(296–304 96ZM651.8)	YVDRFFKRL		human(B*1510, B70)	[Novitsky (2001)]
	• This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort • Four subjects responded to the CTL epitope YVDRFFKTL – all were HLA-B*1510 and also shared HLA-Cw03, suggesting linkage disequilibrium • An HIV-1 B variant of the epitope YVDRFYKTL has been described, and was recognized by CTL from an HIV-1 subtype A-infected patient, and the HLA restriction of the epitope was suggested to be A26 or B70 – HLA-B*1510 is equivalent to the serological specificity HLA B70				

p24(164–172)	p24(164–172)	YVDRFYKTL	HIV-1 infection	human(B70)	[Ferrari (2000)]
• One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles					
p24(166–174)	p24(298–306 LAI)	DRFYKTLRA	HIV-1 infection	human(B*1402)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*1402 epitope					
p24(166–174)	p24(298–306 IIIB)	DRFYKTLRA	HIV-1 infection	human(B14)	[Wilson (1996)]
• Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study • DRFYKILRA, a naturally occurring variant, was found in the mother, and is recognized although less reactive • DQFYKTLRA, a naturally occurring variant, was found in the infant and is not recognized					
p24(166–174)	p24(298–306 IIIB)	DRFYKTLRA	HIV-1 infection	human(B14)	[Cao (1997)]
• The consensus peptide for clades B and D is DRFYKTLRA • The consensus peptide for clades A and C is DRFFKTLRA and it is equally reactive					
p24(166–174)	p24(298–306 HXB2)	DRFYKTLRA	HIV-1 infection	human(B14)	[Yang (1997b)]
• A chimeric universal T-cell receptor was created by linking CD4 or an HIV-specific anti-gp41 Ig sequence to the signaling domain of the T-cell receptor chain ζ, and transducing into CD8+ cells • The response using universal-receptor-bearing CD8+ cells to lyse infected cells *in vitro* was comparable to the natural occurring responses of CTL-clones from HIV+ individuals in terms of kinetics and efficiency • A CTL clone specific for this epitope was used for the comparison					
p24(166–174)	p24( )	DRFWKTLRA	HIV-1 exposed seronegative	human(B14)	[Rowland-Jones (1998a)]
• A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating • The D subtype consensus is identical to the B clade epitope • The A subtype consensus is drFfKtLRA					
p24(166–174)	p24(298–306 LAI)	DRFYKTLRA	HIV-1 infection	human(B14)	[Harrer (1996b)]
p24(166–174)	p24(298–306)	DRFYKTLRA	HIV-1 infection	human(B14)	[Yang (1996)]
• CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL • Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones • The distinction was thought to be due to lower expression of RT relative to Env and Gag • CTL can lyse infected cells early after infection, possibly prior to viral production					
p24(166–174)	p24(298–306)	DRFYKTLRA	HIV-1 infection	human(B14)	[Yang (1997a)]
• CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*					

- CTL produced HIV-1-suppressive soluble factors – MIP-1α, MIP-1β, RANTES, after antigen-specific activation
- CTL suppress HIV replication more efficiently in HLA-matched cells

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p24(166–174) p24(298–306) DRFYKTLRA *in vitro* stimulation human(B14) [Zarling (1999)]

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses
- Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL

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p24(166–174) p24( ) DRFYKLTRA human(B14) [Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective
- HIV-2 sequence: DRFYKSLRA is cross-reactive, [Harrer1993]

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p24(166–174) p24(298–306 IIIB) DRFYKTLRA HIV-1 infection human(B14) [Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- DRFYKILRA and DQFYKTLRA were escape mutants

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p24(166–174) p24( ) DRFYKTLRA HIV-1 infection human(B14) [Goulder (2000a)]

- The CTL-dominant response was focused on this epitope in 2/5 HIV+ individuals who were HLA B14 living in Boston – this epitope did not fall within the three most recognized peptides in the study
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

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p24(166–174) p24( ) DRFYKTLRA HIV-1 infection human(B14) [Goulder (2001b)]

- Epitope name: DA9. Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation

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p24(166–174)	p24(166–174)	DRFYKTLRA	HIV-1 infection	human(B14)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

p24(166–174)	p24(298–306 SF2)	DRFYKTLRA	HIV-1 infection	human(B14)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B14+ individuals that had a CTL response to this epitope broken down by group: 3/3 group 1, 1/2 group 2, and 0/0 group 3

p24(166–174)	p24(298–306)	DRFFKTLRA	HIV-1 exposed seronegative, HIV-1 infection	human(B14)	[Kaul (2001a)]

- Variants DRF(F/W)KTLRA are specific for clades A/B
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B14 women, 0/4 HEPS and 6/7 HIV-1-infected women recognized this epitope, likelihood ratio 14.4, p value 0.004 and HEPS women tended to respond to DLNMMLNIV/DLNTMLNVV, while infected women tended to respond to DRF(F/W)KTLRA
- The dominant response to this HLA allele was to this epitope for all of the 6/7 HIV-1-infected women
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort

p24(166–174)	p24( )	DRFYKTLRA	HIV-1 infection	human(B14)	[Altfeld (2000)]

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual

p24(166–174)	p24( )	DRFYKTLRA	HIV-1 exposed seronegative	human(B14, B*1402)	[Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among B and D clade viruses

- The clade A version of the epitope, DRFFKLTRA, was preferentially recognized by CTL
- This epitope was recognized by two different exposed and uninfected prostitutes

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p24(166–175) p24(298–306 HX10) DRFYKTLRAE HIV-1 infection human(B14) [Wagner (1999)]

- The immunodominant CTL response in a long-term survivor was to this highly conserved and functionally relevant epitope
- By testing mutations in an HXB2 background, it was found that all mutations within the epitope that abrogated CTL recognition also abolished viral infectivity
- The epitope in this study overlaps the major homology region for which highly conserved residues exist in all known lenti- and onco-viruses and yeast transposons
- Patient was part of the study in [Harrer (1996a)]

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p24(173–181) p24(305–313) RAEQASQEV HIV-1 infection human(Cw8) [Lubaki (1997)]

- Eighty-two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response
- Despite this being a well defined conserved epitope, and thought to be presented by B14, none of the 11 gag-specific clones from a B-14 positive subject could recognize either it or p24 PQDLNTMLN
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)

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p24(173–181) ( ) RAEQASQEV HIV-1 infection human( ) [Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was 1/22 HEPS sex worker controls ML1792

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p24(173–181) p24(305–313) RAEQASQEV HIV-1 exposed seronegative, HIV-1 infection human(B14) [Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

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p24(173–181) p24(305–313) RAEQASQEV HIV-1 infection human(B14?) [Price (1995)]

- Study of cytokines released by HIV-1 specific activated CTL
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)

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p24(173–181) p24(305–313) RAEQASQEV HIV-1 infection human(Cw8) [Johnson (1991)]

- Originally reported as HLA-B14 restricted, but subsequently found not to be presented by cells transfected with B14

- Thought to be HLA-Cw8 restricted (C. Brander and B. Walker)

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p24(173–181) p24( ) RAEQASQEV HIV-1 exposed seronegative human(Cw8) [Rowland-Jones (1998a)]

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating
- The A subtype consensus is RAeQAtQEV
- The D subtype consensus is RAEQsQdV
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)

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p24(174–184) p24(306–316 LAI) AEQASQDVKNW HIV-1 infection human(B44) [Mollet (2000)]

- Epitope name: G3. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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p24(174–184) p24(306–316 LAI) AEQASQDVKNW human(B*4402) [Brander & Goulder(2001)]

- C. Brander notes this is a B*4402 epitope

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p24(174–184) p24(306–316 LAI) AEQASQDVKNW human(B*4402,B44) [Brander & Walker(1997)]

- Pers. Comm. from D. Lewinsohn to C. Brander and B. Walker, C Brander *et al*., this database, 1999

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p24(174–184) Gag(306–316) AEQASQEVKNW HIV-1 infection human(B44) [Brodie (1999)]

- The ability of CTL effector cells was studied by expanding autologous HIV-1 Gag-specific CTL *in vitro*, and adoptively transferring them
- The transferred CTLs migrated to the lymph nodes and transiently reduced circulating productively infected CD4+ T-cells, showing that CTL move to appropriate target sites and mediate anti-viral effects

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p24(174–184) p24(306–316) AEQASQEVKNW HIV-1 infection human(B44) [Brodie (2000)]

- Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, co-localizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1α and MIP-1β, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*

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p24(174–184) p24(174–184) AEQASQDVKNW HIV-1 infection human(B44) [Day (2001)]

- B44-restricted CTL response was strongest to this epitope in one individual

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p24(175–186)	p24(307–318)	EQASQEVKNWMT	HIV-1 infection	human(B44)	[Quayle (1998)]
• HIV is found in semen both as cell-associated and cell-free forms, and HIV-specific CTL could be found in the semen of 5/5 men with CD4 greater than 500 – 3 of the men were analyzed in detail and had broad CTL to Gag, Env, and Pol • Two CTL lines from one donor recognized this epitope • Isolation of CTLs specific to HIV in both male and female urinal tracts provide evidence that virus-specific lymphocytes come from the urogenital mucosa, and the authors speculate that CTL in mucosal tissues may be correlated with lower viral load in semen and reduced transmission					
p24(176–184)	p24(308–316 LAI)	QASQEVKNW	HIV-1 infection	human(B*5301)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*5301 epitope					
p24(176–184)	Gag(308–316 HXB2)	QASQEVKNW	HIV-1 infection	human(B*5301)	[Mulligan (2001)]
• Epitope G31 from Patient 07118 with HLA genotypes A*0209, A*3201, B*4002, B*5301, Cw*0202, Cw*0401 • Epitope G31 Patient 07118 has 4 more optimal peptides P55, PIQKETWETW with HLA A*3201; N10, KEKGGLEGL with HLA B*4002; G21 and G22, AEWDRVHPV with HLA B*4002;G43, TERQANFL with HLA B*4002					
p24(176–184)	p24(309–317 LAI)	QASQEVKNW	HIV-1 infection	human(B*5701)	[Goulder (1996b)]
• Recognition of this peptide by two long-term non-progressors • Peptide defined on the basis of B*5801 binding motif, yet not cross-restricted except at high concentrations • Described as B*5701 in C. Brander *et al*., this database, 1999					
p24(176–184)	p24(311–319 LAI)	QASQEVKNW	HIV-1 infection	human(B*5701)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*5701 epitope					
p24(176–184)	p24(308–316 LAI)	QASQEVKNW	HIV-1 infection	human(B53)	[Buseyne (1997)]
• Minimal sequence determined through epitope mapping • This is a relatively conserved epitope • HLA-Cw*0401 was defined as the restricting element, but cells that carry Cw*0401 varied in their ability to present this epitope – this could be the result of diminished cell-surface expression of Cw*0401 in some cells • The HLA presenting molecule for this epitope was originally described as Cw*0401, but subsequent experiments with an HLA B53+ C4- cell line and with C1R cells transfected with HLA-B53 have shown that the HLA restricting element is HLA-B53 (Pers. Comm., Dr. Florence Buseyne, 2000)					
p24(176–184)	( )	QASQEVKNW		(B53)	[Brander & Goulder(2001), Buseyne (1996), Buseyne (1997), Buseyne(1999)]
p24(176–184)	p24( )	QASQEVKNW	*in vitro* stimulation	human(B53)	[Buseyne (2001)]
• Epitope name: QW9. Exogenous presentation or cross-presentation of epitopes by antigen presenting cells (APC) without protein synthesis is an alternative pathway for CTL epitope processing that may be important in the initial generation of viral specific CTL					

- Dendritic cells treated with AZT to inhibit protein synthesis were able to elicit a strong specific CTL response in QASQEVKNW specific CTL clone 141 without protein synthesis, while macrophages demonstrated a decreased presentation efficiency
- Exogenous Gag epitope presentation was Env-dependent and required receptor-dependent fusion

p24(176–184)	p24(308–316)	QATQEVKNW	HIV-1 exposed seronegative, HIV-1 infection	human(B53)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B53 women, 1/2 HEPS and 7/9 HIV-1-infected women recognized this epitope

p24(176–184)	p24(308–316 subtype A consensus)	QATQEVKNM	HIV-1 infection	human(B53)	[Dorrell (2001)]

- In clade A infected Gambians, three HLA-B53 epitopes were defined in Gag p24 using ELISPOT, tetramer, and cytotoxicity assays
- Two of the new epitopes lacked the predicted P2 anchors, DTINEEAAEW and QATQEVKNM, and bound to B53 with high affinity, thus extending the anchor residue motif for B53 and the related B35
- While S, T, and P could all fit into the HLA-B35 or HLA-B53 B pocket and form a hydrogen bond, A would not form a bond, so the authors propose compensatory interactions account for the high affinity of QATQEVKNM for B53
- QATQEVKNM was recognized in 6/7 HLA-B53 subjects
- Cross-recognition of QATQEVKNM was not studied here, but it was noted that both the A, QATQEVKNM, and B, QASQDVKNW, subtype version of this epitope, are also presented by HLA-B57 and B58, common HLA alleles in Africans

p24(176–184)	Gag( )	QASQEVKNW	HIV-1 infection	human(B57)	[Goulder (2001b)]

- Epitope name: QW9. This peptide elicited a weak CTL response during acute infection of patient PI004
- Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond

p24(176–184)	( )	QASQEVKNW		(Cw4)	[Brander & Goulder(2001), Buseyne (1997), Buseyne(1999)]

p24(176–184)	p24(176–184)	QASGEVKNW	HIV-1 exposed seronegative, HIV-1 infection	human(Cw4)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

p24(176–185)	p24(311–319 SF2)	QASKEVKNWV	HIV-1 infection	human(B57)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/2 group 3

p24(177–185)	p24(177–185)	ATQEVKNWM	HIV-1 exposed seronegative, HIV-1 infection	human(B53)	[Kaul (2001a)]

- Variants A(T/S)QEVKNWM are specific for the A/B clades
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B53 women, 1/2 HEPS and 5/9 HIV-1-infected women recognized this epitope
- The dominant response to this HLA allele was to this epitope in the 1/2 HEPS cases and in only one of the 5/9 HIV-1-infected women

p24(180–189)	p24(313–322)	EVKNWMTETL	HIV-1 exposed seronegative, HIV-1 infection	human(B53)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

p24(181–190)	p24(313–322 LAI)	VKNWMTETLL		human(B8)	[Brander & Walker(1996)]

- P. Johnson, pers. comm.

p24(191–205)	p24(191–205)	VQNANPDCKTILKAL	HIV-1 infection	human(B51)	[Ferrari (2000)]
• One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles					
p24(191–205)	p24(323–337)	VQNANPDCKTILKAL	HIV-1 infection	human(B8)	[Nixon & McMichael(1991)]
• Two CTL epitopes defined (see also p17(21-35))					
p24(191–205)	p24(325–339 SF2)	VQNANPDCKTILKAL	HIV-1 infection	human(B8)	[Goulder (1997a), Phillips (1991)]
• Longitudinal study of CTL escape mutants in people with the appropriate HLA types – little variation was observed in the immunodominant B27 epitope, relative to the B8 epitopes, which varied over time • [Goulder (1997a)] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA B27 patients					
p24(191–210)	p24(323–342 SF2)	VQNANPDCKTILKAL-GPAAT	HIV-1 infection	human( )	[Lieberman (1997a)]
• Of 25 patients, most had CTL specific for more than one HIV-1 protein • Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag • Three of these 12 had CTL response to this peptide • The responding subjects were HLA-A3, A24, B8, B55; HLA-A1, A11, B8, B27					
p24(191–210)	p24(323–342 SF2)	VQNANPDCKTILKAL-GPAAT	HIV-1 infection	human( )	[Lieberman (1997b)]
• CTL expanded *ex vivo* were later infused into HIV-1 infected patients					
p24(193–201)	Gag(327–335 SF2)	NANPDCKTI	HIV-1 infection	human(B*5101)	[Tomiyama (1999)]
• HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995) • 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3% • Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed • Four of the six epitopes were highly conserved among B subtype sequences, NANPDCKTI is conserved					
p24(193–201)	p24(325–333)	NANPDCKTI?	HIV-1 infection	human(B51)	[Betts (2000)]
• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant • Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes • 3/11 of the HLA A2+ individuals were HLA B51 and two of these responded to this epitope as well as to other epitopes					
p24(193–201)	p24(324–335 IIIB)	NANPDCKTI	HIV-1 infection	human(B51)	[Wilson (1999a)]
• This study describes maternal CTL responses in the context of mother-to-infant transmission					

- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- No variants of this epitope were found in a non-transmitting mother that had a CTL response to this epitope

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p24(193–201) p24(323–333) NANPDCKTI HIV-1 infection human(B51) [Oxenius (2000)]

- Epitope name: NAN. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- None of the 8 study subjects recognized this epitope but none were HLA B51+

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p24(193–201) p24(191–205) NANPDCKTI HIV-1 infection human(B8) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p24(195–202) p24(323–342) NPDCKTIL HIV-1 infection human(B35) [Bernard (1998)]

- This study focuses on six rare HIV-infected long-term survivors who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs
- Epitope sequences were deduced from larger reactive peptides based on HLA binding motifs – XPXXXXXL is a B35 binding motif

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p24(197–205) p24(329–337 LAI) DCKTILKAL human(B*0801) [Brander & Goulder(2001)]

- C. Brander notes this is a B*0801 epitope

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p24(197–205) p24(329–337 LAI) DCKTILKAL human(B8) [Sutton (1993)]

- Predicted epitope based on B8-binding motifs, from larger peptide VQNANPDCKTILKAL

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p24(197–205) p24(329–337) DCKTILKAL HIV-1 infection human(B8) [Nowak (1995)]

- In a longitudinal study of CTL response and immune escape – the variant DCRTILKAL was also found, binds to B8, but is not recognized

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p24(197–205) p24(329–337) DCKTILKAL human(B8) [McAdam (1995)]

- Defined as minimal epitope by titration and binding studies

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p24(197–205) p24(197–205) DCKTILKAL human(B8) [Goulder (1997g)]

- Included in a study of the B8 binding motif

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p24(197–205) p24(329–337) DCKTILKAL HIV-1 infection human(B8) [Oxenius (2000)]

- Epitope name: DCK. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- This epitope was recognized at a low level by only 1 of the 7/8 study subjects that were HLA B8
- Patient SC12(HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKKKYKLK – GEIYKRWII and GGKKKYKLK responses were stimulated by a brief period off therapy

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p24(197–205) p24(197–205) DCKTILKAL HIV-1 infection human(B8) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p24(197–205) p24(197–205) DCKTILKAL HIV-1 infection human(B8) [Day (2001)]

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual

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p24(211–230) p24(345–364 SF2) LEEMMTACQGVGGPG-HKARV HIV-1 infection human( ) [van Baalen (1993)]

- Gag CTL epitope precursor frequencies estimated, peptide mapping

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p24(211–230) p24(343–362 SF2) LEEMMTACQGVGGPG-HKARV HIV-1 infection human(B7) [McAdam (1998)]

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p24(211–231) p24(343–362 SF2) LEEMMTACQGVGGPG-HKARVL HIV-1 infection human( ) [Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag
- One of these 12 had CTL response to this peptide
- The responding subject was HLA-A1, A2, B50, B57

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p24(217–227) p24(349–359 IIIB) ACQGVGGPGHK HIV-1 infection human(A*1101) [Brander & Goulder(2001)]

- C. Brander notes this is an A*1101 epitope

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p24(217–227) p24(349–359 IIIB) ACQGVGGPGHK HIV-1 infection human(A11) [Sipsas (1997)]

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by three lab workers accidentally infected with HIV-1 IIIB
- ACQGVGGPSHK, a variant found in HIV RF, was also recognized

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p24(217–227) p24( ) ACQGVGGPGHK HIV-1 infection human(A11) [Goulder (2000a)]

- The CTL-dominant response was focused on this epitope in an HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study

- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa

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p24(217–227) p24(349–359) ACQGVGGPGHK HIV-1 infection human(A11) [Oxenius (2000)]

- Epitope name: ACQ. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- Both of the 2/8 HLA-A11 study subjects recognized this CTL epitope
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKR-WII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197
- Patient SC18(HLA A2/11, B8/44, Cw06/0701, DR3/7, DR52/53, DQ2) recognizes the epitopes ACQGVGGPGHK, QVPLRPMTYK, AVDLSHFLK, and one called QIY but not fully described – he had brief therapy upon seroconversion and has had low viral load during 600 days of follow up

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p24(217–227) p24(216–226) ACQGVGGPGHK HIV-1 infection human(A11) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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p24(217–227) p24(349–359 SF2) ACQGVGGPGHK HIV-1 infection human(A11) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 2/2 group 3

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p24(221–231) p24(353–363 LAI) VGGPGHKARVL HIV-1 infection human(B7) [Mollet (2000)]

- Epitope name: G1. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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p24(223–231)	p24(223–231 SF2)	GPGHKARVL	HIV-1 infection	human(B*0702)	[Altfeld (2001a)]

- Epitope name: GL9. HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses is underestimated if accessory proteins are not included in the study
- The response to GPGHKARVL was dominant

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p24(223–231)	p24(355–363 LAI)	GPGHKARVL	HIV-1 infection	human(B7)	[Goulder (1997e), Goulder (1997a)]

- Identical twin hemophiliac brothers were both infected with the same batch of factor VIII
- One had a strong response to this peptide, the other a weak response
- [Goulder (1997a)] is a review of immune escape that summarizes this study

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p24(223–231)	p24( )	GPSHKARVL	HIV-1 infection	human(B7)	[Goulder (2000a)]

- The CTL-dominant response was focused on this epitope in an HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
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p24(223–231)	p24( )	GPSHKARVL	HIV-1 infection	human(B7)	[Goulder (2000a)]

- The CTL-dominant response was focused on this epitope in an HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses
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p24(223–231)	p24(223–231 SF2)	GPGHKARVL	HIV-1 infection	human(B7)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response

	• Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 1/4 group 1, 2/3 group 2, and 0/1 group 3				
p24(223–231)	p24(223–231)	GPGHKARVL	HIV-1 infection	human(B7)	[Day (2001)]
	• The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP) • Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person • Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes • An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes • The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested • The B7-restricted CTL response was highly variable and there was no clearly dominant epitope				
p24(223–232)	Gag( )	GPGHKARVLA		human(B7)	[De Groot (2001)]
	• The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes • A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay • GPGHKARVLA was confirmed as an HLA-B7 epitope in this study, and had been previously published				
p24( )	p24( )		HIV-1 infection	human( )	[Goulder (2000a)]
	• The CTL-dominant response was focused on this epitope in an HIV+ South African – this epitope did not fall within the five most recognized peptides in the study • Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPG-GKKKYKLK(p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses • Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa				

Table 4: **p2p7p1p6**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
p2p7p1p6(1–7)	Gag( )	VLAEAMSQV	HIV-1 infection	human(A*0201)	[Altfeld (2001d)]
• Epitope name: Gag-386. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested • Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2) • VLAEAMSQV binds to all five HLA-A2 supertype alleles tested: A*0201, A*0202, A*0203, A*0206 and A*6802 (highest affinity) • 4/22 individuals with chronic HIV-1 infection recognized this epitope, and it was immunodominant in 3/4 by ELISPOT • 0/12 acutely infected individuals recognized this epitope				
p2p7p1p6(1–7)	Gag(397–405)	VLAEAMSQV	HIV-1 infection	human(A2 supertype)	[Propato (2001)]
• Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes • Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs • A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus • This epitope can bind five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)				
p2p7p1p6(5–13)	Gag( )	SQVTNPANI	Vaccine	murine BALB/c(H-2D^b)	[Paliard (1998)]
Vaccine: *Strain:* SF2 *HIV component:* Gag • HIV-1(SF2)p55gag vaccination of H-2 mice activates a CTL response against this epitope • CTL that recognized SQVTNPANI in the context of H-2D^b cross-reacted with H-2 alloantigens H-2L^d and an unidentified self-peptide • A postulate: heterozygosity at the MHC level could prevent the maturation of some T-cell receptor combinations for foreign peptide and self-MHC constructs because of thymic depletion and tolerance					
p2p7p1p6(18–37)	Gag( )	SNFKGNKRMVKCFNC-GKEGH		human(A*02011)	[Novitsky (2001)]
• This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort • 4/8 individuals (50%) who were positive for HLA-A*02011 responded to the peptide SNFKGNKRMVKCFNCGKEGH					
p2p7p1p6(55–70)	p15(446–460 BRU)	KEGHQMKDCTERQAN-F	HIV-1 infection	human(A2)	[Claverie (1988)]
• One of four epitopes first predicted, then subsequently shown to stimulate an HLA-A2 restricted CTL line					

p2p7p1p6(64–71)	Gag(427–434 HXB2)	TERQANFL	HIV-1 infection	human(B*4002)	[Mulligan (2001)]
	• Epitope G43 from Patient 07118 with HLA genotypes A*0209, A*3201, B*4002, B*5301, Cw*0202, Cw*0401 • Epitope G43 Patient 07118 has 4 more optimal peptides P55, PIQKETWETW with HLA A*3201; N10, KEKGGLEGL with HLA B*4002; G21 and G22, AEWDRVHPV with HLA B*4002;G31, QASQEVKNW with HLA B*5301				
p2p7p1p6(83–97)	p15(418–433 BRU)	GNFLQSRPEPTAPPF	HIV-1 infection	human(A2)	[Claverie (1988)]
	• One of four epitopes first predicted, then subsequently shown to stimulate an HLA-A2 restricted CTL line				
p2p7p1p6(118–126)	p2p7p1p6(118–126)	KELYPLTSL		human(B*4001(B60))	[Brander & Goulder(2001)]
	• C. Brander notes that this is a B*4001 epitope				
p2p7p1p6(121–130)	Gag(484–493)	YPLTSLRSLF	HIV-1 infection	human(B7)	[Jin (2000b)]
	• This B7 epitope is one of three subdominant CTL responses detected in a long-term non-progressor • A dominant B7 epitope was defined using conventional methods, and three additional sub-dominant HLA B7 epitopes were defined by first using a non-anchor based strategy, EpiMatrix, to identify 2078 possible epitopes in the autologous HIV-1, followed by B7 anchor residue prediction to narrow the set to 55 peptides for experimental testing				

Table 5: **p55**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
p55(357–372)	Gag(357–372 LAI)	GHKARVLAEATLSQVN	HIV-1 infection	human( )	[Buseyne (1993a)]
	• Vertical transmission of HIV ranges from 13% to 39%				
	• Primary assays showed cytotoxic activity against at least one HIV protein was detected in 70% of infected children				
	• Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures				
	• Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag				

Table 6: **Gag**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Gag(77–85)	Gag(77–85)	SLYNTVATL		human(HLA-A201)	[Sandberg (2000)]
• This epitope served as a positive control in a study comparing peptide binding affinity to HLA-A201 to CTL responses upon vaccination with a nef DNA vaccine					
Gag(223–231)	( )	GPGHKARVL		(B7)	[Brander & Goulder(2001), Goulder(1999)]
Gag( )	Gag( )		Vaccine	Rhesus macaque( )	[Paliard (2000)]
Vaccine: *Vector/type:* virus-like particle *HIV component:* gag					
• CTLs primed by HIV-1 p55 gag virus-like particle (VLP) vaccination recognized epitopes in four different 20 amino acid peptides p17/4, p17/8, p24/13 and p14/9					
• Cytotoxic T-cell response lasted greater than 8.5 months					
Gag( )	Gag( )		HIV-1 infection	human( )	[Wasik (2000)]
• HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of β-chemokines and IL-2 relative to other HIV+ infants					
• No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors					
• CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccinia/HIV constructs					
Gag( )	Gag( )		Vaccine	human( )	[Salmon-Ceron (1999)]
Vaccine: *Vector/type:* canarypox *Strain:* LAI, MN *HIV component:* gp41, Gag, Pro, V3					
• The vaccine used was a rec canarypox with HIV-1 gp120 MN, tm/gag/protease LAI (vCP205), alone or with p24E-V3 MN synthetic peptide (CLTB-36))					
• Twenty HIV negative subjects were vaccinated in phase I trial with combinations of vCP205 and CLTB-36					
• Immunization with vCP205 induced HIV-1-specific ABs to gp160, V3, and p24 antigens, and CTL immune responses against vCP205 were detected after the fourth immunization in 33% of the subjects against Env, Gag and Pol, but the CLTB-36 peptide did not produce AB or CTL immune responses against p24 or gp160					
Gag( )	p24( )		Vaccine	human( )	[Klein (1997)]
Vaccine: *Vector/type:* virus-like particle *HIV component:* p24, p17					
• Immunization of HIV+ people with an HIV-1 p17/p24 Ty virus-like particle (p24-VLP) resulted in a marginal, short-lived increased proliferative response to p24 and p17 and a transient elevation in viral load					
• Two of four subjects that received 500 or 1000 μg of p24-VLP had an increase in gag-specific CTL					

Gag( )	p24( )	Vaccine	murine, baboon( )	[O'Hagan (2000)]

Vaccine: *Vector/type:* DNA *Strain:* SF2 *HIV component:* gp120, p24 *Stimulatory Agents:* PLG-microparticle, MF59 adjuvant

- PLG (Polylactide co-glycolide polymer) microparticles administered in MF59 emulsion induced gp120 Ab responses and CTL immune responses against p24 gag

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Gag( )	Gag( )	HIV-1 infection	human( )	[Lubaki (1999)]

- Three strategies were used to analyze CTL activity: area under the net HIV-specific lysis curve (ACU), linear regression (LR) of net specific lysis, and the standard method, lytic units (LU20)
- A correlation between low HIV plasma viral load and increased levels of HIV-specific Gag and Nef CTL activity was observed using ACU and LR, but not LU20

Gag( )	Gag( )	HIV-1 infection	human( )	[Kalams (1999a)]

- The presence of HIV-1 p24-specific proliferative responses was positively correlated with Gag-specific memory CTL and negatively correlated with viral load in untreated subjects
- Gag proliferative responses were the most readily detected – Gag CTL responses were the only responses with a significant correlation with Gag stimulated help, although there was a positive trend with Nef, Env and RT

Gag( )	p55( )	HIV-1 infection	human( )	[Greenough (1999)]

- 7/128 HIV-1 infected hemophiliacs were identified as long-term non-progressors (LTNPs) and were monitored for viral and host immune parameters over 15 years – LTNPs maintained a low viral load, high frequencies of CTL precursors directed against Gag antigen and low levels of HIV-specific effector CTL activity – effector cell activity suggests low level ongoing viral replication

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Gag( )	Gag( )	HIV-1 infection	human( )	[Trickett (1998)]

- Twelve HIV-1 infected patients were re-infused with their own lymphocytes, cryopreserved from an earlier time point in the infection
- Improvement in CD4+ and CD8+ T-cells was seen in 7/12, and an increase in the CTL response to Gag was seen in one patient

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Gag( )	Gag( )	HIV-1 infection	human( )	[Betts (1999)]

- This study demonstrated an inverse correlation between HIV Type I plasma viral load and CTL activity directed against HIV-1 Pol, and stronger combined effects of Pol- and Env-specific CTL, in long-term survivors (LTS) of HIV-1 infection

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Gag( )	Gag( )	HIV-1 infection	human( )	[Legrand (1997)]

- Seventeen recently infected patients were tested for CTL response to HIV proteins Env, Gag, Pol, Rev, Nef, Vif and Tat
- An early response (within a month following PI) was noted in 87% of the subjects to Gag, 75% to Env, and 50% to Nef
- Early responses to Pol, Rev, Vif and Tat were rare

Gag( )	Gag( )	HIV-1 infection	human( )	[Betts (1997)]

- 6/8 individuals from Zambia infected with C clade virus had CTL that were able to make response to B clade HIV-1 IIIB vaccinia-expressed Gag, Pol and Env proteins
- A vigorous cross-clade response was not limited to a particular protein, and the level of recognition of different proteins varied among the six patients

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Gag( ) Gag( ) HIV-1 infection human( ) [De Maria (1997)]

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T-cell function
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels

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Gag( ) Gag( ) Vaccine human( ) [Belshe (1998)]

Vaccine: *Vector/type:* canarypox prime with rgp120 boost *Strain:* MN, LAI, SF2 *HIV component:* gp120, gp41, Gag, Protease

- The live canarypox vaccine ALVAC-HIV(vCP205) carrying MN gp120, LAI gp41, Gag and Protease, and boosted with SF-2 rpg120, was given to HIV-1 seronegative volunteers – HIV-specific Env or Gag CD8+ CTL were detected in 64% of the volunteers

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Gag( ) Gag( ) HIV-1 infection human( ) [Buseyne (1998a)]

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load

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Gag( ) Gag( ) HIV-1 infection human( ) [Buseyne (1998b)]

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes

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Gag( ) Gag( ) HIV-1 exposed seronegative human( ) [Goh (1999)]

- 13/37 exposed uninfected individuals with repeated high-risk sexual exposure had HIV-1 specific CTL against Env, Gag, Pol, or a combination of proteins – CTL activity was correlated with a CCR5 wildtype genotype
- In this group, the highest CTLp frequencies were directed at Gag, but the most common response was to Env and four individuals had responses to multiple HIV-1 proteins

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Gag( ) Gag( ) Vaccine human( ) [Evans (1999)]

Vaccine: *Vector/type:* canarypox *HIV component:* gp120, gp41, Gag, Pro, Nef, RT

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination

---

Gag( ) p17( ) HIV-1 infection human( ) [Kuiken (1999)]

- A correlation between conserved regions of p17 or Nef and CTL epitope density was noted – the authors suggest that this may be due to a biological reason such as epitope processing, or may possibly be an artifact of experimental strategy for epitope definition such that conserved epitopes would tend to be identified because they would be more likely to be cross-reactive with the test reagents
- In contrast to p17 and Nef, p24 is a more conserved protein and known epitopes are evenly distributed across p24

Gag( ) Gag( ) Vaccine Macaca nemestrina( ) [Kent (1998)]

Vaccine: *Vector/type:* DNA prime with vaccinia boost *Strain:* LAI *HIV component:* Env, Gag

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T-cell immunity than either vaccine alone
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env. The T help response happened despite a decrease in antibody titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced

---

Gag( ) Gag/Pol( ) Vaccine human( ) [Salmon-Ceron (1999)]

Vaccine: *Vector/type:* canarypox *Strain:* MN, LAI *HIV component:* gp120, gp41, Gag, Protease

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy, uninfected volunteers

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Gag( ) Gag/Pol( ) Vaccine chimpanzee( ) [Kim (1998)]

Vaccine: *Vector/type:* DNA *HIV component:* Env, Gag, Pol *Stimulatory Agents:* CD86, CD80

- The study explores the use of co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses

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Gag( ) Gag( ) HIV-1 infection human( ) [Aladdin (1999)]

- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death

---

Gag( ) Gag( ) Vaccine Rhesus macaque( ) [Akahata (2000)]

Vaccine: *Vector/type:* DNA *Strain:* ZF1 *HIV component:* complete genome

- Rhesus macaques were vaccinated by i.m. injection with naked plasmid DNA carrying an HIV-1 complete genome vaccine, strain ZF1, with a mutated zinc finger in the nucleocapsid to prevent packaging
- Env and Gag specific CTL, but no antibody responses, were induced in 2/4 vaccinated monkeys (MM145 and MM153)
- 2/4 monkeys (MM146 and MM143) produced antibodies against p24 and/or gp160, but no CTL response
- PBMC from all vaccinated monkeys produced IFN-γ, in response to HIV-1 gp160, indicating a Th response – this response was 5 times higher in MM145, the animal with the strongest CTL response
- 4 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM145 and MM153 (with a homologous Env) decreased to near or below the detection limit
- 6-8 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM146 and MM143 decreased near or below the detection limit

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Gag( ) Gag( ) HIV-1 infection human( ) [Salerno-Goncalves (2000)]

- A general test of CD8 anti-viral activity was developed based on proviral load of coculture of autologous CD8+ cells with CD4+ cells after homogeneous superinfection with NSI virus
- Significantly decreased CD4+ T-cell proviral loads were found in 12 HIV+ slow progressors relative to 10 rapid progressors

- Significant CD8+ mediated cytotoxicity directed against autologous cells infected with vaccinia carrying the HIV-1 gag gene was observed in slow progressors in contrast to rapid progressors, but no correlation was found between plasma viral load in 22/22 asymptomatic HIV infected individuals

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Gag( ) Gag( ) none HIV-1 infection human( ) [Young (2001)]

- Addition of recombinant human IL-12 (rhIL-12) to cultures increased HIV-specific lysis of HIV-Gag, Pol and gp120 vaccinia expressed antigens (11/15 tested increased lysis by > 5%) if the culture was derived from HIV+ individuals who had > 500 CD4 cells/μl
- 2/10 individuals with <200 CD4 cells/μl, and 3/10 individuals with 200-500 CD4 cells/μl, had an increase of >5% upon treatment of the culture with rhIL-12, so a few individuals in late stage disease had CD8 cells that maintained responsiveness to rhIL-12

Gag( ) ( ) none HIV-1 infection murine( ) [de Quiros (2000)]

- CB-17 SCID-Hu mice engrafted with peripheral blood mononuclear cells of four long-term nonprogressors (viral load < 50 copies/ml) displayed resistance to challenge with HIV-1 SF162, mediated by CD8+ T-cells and associated with proliferation in response to p24 – these patients did not have a higher level of HIV-1 specific immunity *in vitro*, so the mechanism is unknown

---

Gag( ) Gag( ) HIV-1 infection human( ) [Cao (2000)]

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, RT or Nef from HIV-1 clades A, B, and D
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent-specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype

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Gag( ) Gag( ) none HIV-1 infection human( ) [White (2001)]

- HIV-specific CTL activity was detected in the female reproductive tract of only 1/3 HIV-infected women who underwent a hysterectomy, although CTL could be identified in the PBMC of all three women

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Gag( ) Gag( ) none HIV-1 infection human( ) [Chun (2001)]

- Suppression of viral replication in the resting CD4+ T-cell reservoir by autologous CD8+ T-cells via CD4+/CD8+ cell contacts was observed in long-term nonprogressors and patients undergoing antiretroviral treatment, but this activity appears to be independent of Gag-specific CTL activity

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Gag( ) Gag( ) HIV-1 infection human( ) [Jin (2000a)]

- The CTL precursor level (CTLp) was measured in long term non-progressors (LTNP) with low viral load using limiting dilution analysis and measuring CTL against Env Gag and Pol expressed in vaccinia in autologous targets
- LTNPs have high memory CTL numbers and low viral load

Gag( ) Gag( ) HIV-1 exposed seronegative human( ) [Rowland-Jones (2001)]

- This is a review that summarizes observations about HIV-specific CTL found in the HIV-1 exposed persistently seronegative (HEPS) population
- The CTL responses assayed by ELISPOT and by CTL precursor frequencies by limiting dilution analysis indicate that CTL in HEPS individuals tend to be of a lower magnitude than in chronic HIV-1 infections – the responses in HEPS cases are below the level of detection by tetramer assays

- CD8+ CTL responses tend to be detectable in HEPS subjects only if they are recently exposed, and the response diminishes if exposure is reduced – it is not clear if there is a stable memory population in HEPS cases
- CD8+ CTL responses in the HEPS population are associated with HIV-1 specific CD4+ T-cell responses, assayed by proliferation assays, IL-2 secretion, and ELISPOT, and the authors consider the possibility that HIV-1-specific T-help responses improve the "quality" of the CD8+ response in HEPS individuals relative to HIV-1 infected individuals, who tend to have a poor HIV-1-specific T-help response
- HIV-1 specific CD8+ CTL responses in HIV-1 infected individuals show reduced levels of perforin, and the T-cells may not mature properly, and although similar studies have not been conducted in HEPS individuals this is considered as a possible difference in the CTL immune response in HEPS and HIV-1 infected people

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Gag( ) | Gag( ) | HIV-1 infection | human(A*0201, Cw*08) | [Shacklett (2000)]

- HIV-1 specific, MHC class I-restricted CTL killing was detected in duodenal and rectal gut associated lymphoid tissue (GALT) sites from three infected individuals – the distribution of class I restricted CTL was different in the peripheral blood samples and GALT samples

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Gag( ) | p24( ) | Vaccine | murine(H-2^d) | [Qiu (2000)]

Vaccine: *Vector/type:* DNA *HIV component:* gag

- Mice were injected with plasmid DNA at 0, 2 and 4 weeks and lymphocyte proliferation was measured after 6 weeks with recombinant p24 protein
- Secreted HIV-1 Gag expression vectors generated a stronger response than standard Gag or cytoplasmic Gag expression vectors
- IFN-γ levels were increased compared to an undetectable IL-4 response
- CTL levels were also increased in secreted Gag expression vaccination studies

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Gag( ) | Gag( ) | Vaccine | murine(H-2^d) | [Huang (2001)]

Vaccine: *Vector/type:* DNA *Strain:* gag HxB2, pol NL43 *HIV component:* Gag, Pol

- Mice were immunized with four humanized DNA constructs: GagPol, that would form a pseudoparticle carrying Gag and Pol, Gag, Pol or a GagPol fusion construct
- The GagPol pseudoparticle, Gag and GagPol fusion construct all elicited strong anti-Gag CTL, but only the GagPol fusion construct elicited strong anti-Pol CTL

Gag( ) | p24( ) | Vaccine | murine(H-2^b, H-2^d, H-2^k) | [Iroegbu (2000)]

Vaccine: *Vector/type:* DNA *HIV component:* p17/p24

- The p24 sequence is more conserved than is p17 within patient, and nonsynonymous substitutions are spread evenly throughout its coding regions, not concentrated in CTL epitopes
- Minor changes in p24 did not alter the immunogenicity in H-$2^{b,d,k}$ mice, while changes in p17 (92% similarity) did alter immunogenicity

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Gag( )	Gag( )		Vaccine	murine(H-2^{bxd})	[Otten (2000)]

Vaccine: *Vector/type:* DNA, vaccinia *Strain:* SF2 *HIV component:* codon-optimized gag and pol

- CB6F1 were primed with gag DNA by i.m. injection and challenged with vaccinia expressing Gag/Pol (rVVgag-pol)
- Gag-specific CTL responses were detected by IFNγ secretion in the spleen, independent of the route (intraperitoneal, intranasal or intrarectal) of rVV gag-pol challenge
- The gag DNA vaccine induced CTL responses in 4/4 monkeys 2 weeks post immunization, but antibody responses were detected in only 1/4 monkeys after 3 immunizations
- CTL cross-reactivity against Gag sequences 1–80, 254–323, and 421–496 was observed, suggesting multiple CTL epitope recognition

---

Gag( )	Gag( )		Vaccine	Rhesus macaque, murine(H-2^{d})	[zur Megede (2000)]

Vaccine: *Vector/type:* vaccinia *Strain:* SF2 *HIV component:* Gag, Protease, codon-optimized

- Sequence-modified Rev-independent gag and gag-protease gene constructs lead to increased expression levels and elevated CTL and antibody immunogenicity in BALB/c and CB6F1 mice
- A CTL response in mice could be detected after a single immunization with codon-optimized gag, using 2 ng of plasmid; wild type gag required 200 ng to detect a response
- Recognition of 3 different Gag peptide pools was observed, indicating a polyclonal CTL response
- Significant gag-specific CTL responses were detected in 4/4 rhesus monkeys, in contrast to 1/4 using wildtype gag

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Gag( )	p24( )		Vaccine	murine(H-2^{d})	[Halim (2000)]

Vaccine: *Vector/type:* coxsackievirus *HIV component:* partial p24, polyepitope

- An avirulent recombinant coxsackievirus (CB4-P) construct was generated that can express p24 Gag sequences – CB4-P is attenuated even in immunodeficient mice and T help responses can be elicited from peptides embedded in a surface loop of the VP1 capsid
- This paper describes the vaccine strategy and generation of constructs, and employs amino-terminal fusion of Gag sequences to the viral polyprotein with subsequent cleavage to elicit CTL responses via MHC class I presentation in BALB/c mice

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Gag( )	Gag( )	none	Vaccine	murine(H-2^{d}, H-2^{b})	[Mata (2001)]

Vaccine: *Vector/type:* Listeria monocytogenes *Strain:* HXB2 *HIV component:* Gag

- BALB/c and C57BL/6 mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways
- CD4+ Th1 T-cells mediated the Gag specific immunological protection in mice immunized with Lm-Gag and challenged with vaccinia-Gag
- Gag-specific CTL may enhance viral clearance via IFN-γ secretion, but are not essential for immunity

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Gag( )	Gag( )	none	Vaccine	murine(H-2^d, H-2^b)	[Mata & Paterson(2000)]

Vaccine: *Vector/type:* Listeria monocytogenes *Strain:* HXB2 *HIV component:* Gag

- BALB/c and C57BL/6 mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways
- This article is a review of L. monocytogenes biology and its potential as a vaccine vector for HIV, comparing to other vector systems, and discussing CD4+ Th1 T-cells mediated Gag specific immunological protection in mice and the Gag CTL response

Table 7: **Gag/Pol**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Gag/Pol( )	Gag/Pol( )		Vaccine	Macaca nemestrina( )	[Kent (2000)]
Vaccine: *Vector/type:* fowlpoxvirus *Strain:* ARV-2,SF2 *HIV component:* Gag, Pol *Stimulatory Agents:* IFN-γ					
• Vaccination with FPV Gag/Pol-IFN-γ increased HIV-1 specific CTL and T-cell proliferative responses to Gag/Pol antigens, respectively, in infected Macaca nemestrina					
• HIV-1 viral loads remained low and unchanged following vaccinations					
Gag/Pol( )	RT( )		Vaccine	murine( )	[Kim (1997c)]
Vaccine: *Vector/type:* DNA *HIV component:* Gag, Pol, Vif, Env *Stimulatory Agents:* B7, IL-12					
• A Gag/Pol or Env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules CD86, gave a dramatic increase in both the cytotoxic and proliferative responses in mice					
• When CD86 was present, CTL response could be detected even without *in vitro* stimulation					
Gag/Pol( )	RT( )		HIV-1 infection	human( )	[Gamberg (1999)]
• 13/13 subjects with advanced HIV infections showed CD8 T-cell proliferation and differentiation of CTL *in vitro*, and six individuals showed HIV-specific responses to Gag, Pol, Env or Nef antigens					
• Data suggests that the functional and genetic integrity of the CD8 T-cell repertoire (TCR Vβ gene intrafamily genetic diversity) remains intact through advanced HIV infection, although HIV-specific CTL activity decreases					

Table 8: **Protease**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Protease(3–11)	RT(71–79 clades A, B, D)	ITLWQRPLV		human(A*6802)	[Brander & Goulder(2001)]
	• C. Brander notes this is an A*6802 epitope				
Protease(3–11)	Protease(71–79 LAI)	ITLWQRPLV		human(A*6802, A*7401, A19)	[Dong(1998)]
	• Predicted on binding motif, no truncations analyzed • clade A/B/D consensus, S. Rowland-Jones, pers. comm.				
Protease(3–11)	RT(71–79 clades A, B, D)	ITLWQRPLV		human(A*7401)	[Brander & Goulder(2001)]
	• C. Brander notes this is an A*7401 epitope				
Protease(3–11)	Pol(59–65)	ITLWQRPLV	HIV-1 infection	human(A28)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
Protease(3–11)	RT(71–79 LAI)	ITLWQRPLV	HIV-1 infection	human(A28 supertype)	[Mollet (2000)]
	• Epitope name: P2. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses • In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished • Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change				
Protease(3–11)	Pol( )	ITLWQRPLV	HIV-1 exposed seronegative, HIV-1 infection	human(A74)	[Kaul (2001a)]
	• ITLWQRPLV cross-reacts with clades A, B and D • ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers				
Protease(11–20)	Pol(91–100)	VTILIGGQLK	HIV-1 infection	human(A3 supertype)	[Propato (2001)]
	• Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes • Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs				

- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

Protease(12–20) Pol(92–100) TIKIGGQLK HIV-1 infection human(A3 supertype) [Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

Protease(30–38) Pol( ) DTVLEEMNL HIV-1 exposed seronegative human(A*6802) [Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among B and D clade viruses
- The clade A version of the epitope: DTVLEDINL
- This epitope was recognized by two different exposed and uninfected prostitutes
- This epitope was identified by screening 49 HIV-1 peptides with the predicted A*6802 anchor residue motif x[VT]xxxxxx[VL]

Protease(30–38) pol( ) DTVLEDINL HIV-1 exposed seronegative human(A*6802) [Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells
- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women

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Protease(30–38) RT(85–93 clade D) DTVLEEWNL human(A*6802) [Brander & Goulder(2001)]

- C. Brander notes this is an A*6802 epitope

Protease(30–38) Pol( ) DTVLEDINL HIV-1 infection human(A*6802) [Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- DTVLEDINL was recognized in 3 of the 6 women (ML857, ML1203, and ML1707), and the response was present in the last available sample prior to seroconversion, 3-7 months
- In each of the three women, 20/20 sequences of the infecting strain had no substitutions in this epitope, all were DTVLEDINL, so there was no evidence for escape

- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized in 3/22 HEPS sex worker controls, ML851, ML1432, and ML1601

Protease(30–38)	Pol(85–93)	DTVLEDINL	HIV-1 exposed seronegative, HIV-1 infection	human(A*6802)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-A*6802 women, 11/12 HEPS and 6/11 HIV-1-infected women recognized this epitope likelihood ratio 4.4, p value 0.08, and HEPS women tended to respond to DTVLEDINL, infected women tended to respond to ETAYFYILKL
- The dominant response to this HLA allele was to this epitope in 10 of the 11/12 HEPS cases, but in only 4 of the 6/11 HIV-1-infected women
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort
- Four epitopes were considered to be “resistant epitopes”, as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILKD/EPVHGV in RT, A*6802 DTVLEDINL in Protease, B14 DLNM/TLNI/VV in p24 and B18 FRDYVDRFY/FK also in p24
- Subject ML 857 shifted from an A*6802 DTVLEDINL and B35 H/NPDIVIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion, and the loss of the pre-seroconversion response was not due to sequence variation within these epitopes
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV
- Subject ML 1707 started with a CTL response to A*6802 DTVLEDINL prior to seroconversion, and switched to A*6802 ETAYFILKL and A24 RDYVDRFFKTL post-seroconversion, and the loss of the pre-seroconversion response was not due to sequence variation within the epitope
- Subject ML 1830 made no detectable response prior to seroconversion, but responded to A*6802 DTVLEDINL and A*6802 ETAYFILKL post-seroconversion

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Protease(45–54)	Pol(125–134)	KMIGGIGGFI	HIV-1 infection	human(A2 supertype)	[Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus

- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)

Protease(75–84) Protease(75–84 MN) VLVGPTPVNI *in vitro* stimulation human(A*0201) [Konya (1997)]

- Peptide predicted to be reactive based on HLA-A*0201 binding motif
- Peptide could stimulate CTL in PBMC from 5/6 seronegative donors
- Peptide located in a highly conserved region of protease
- Both 9-mer and 10-mer could stimulate CTL: VLVGPTPVNI and LVGPTPVNI
- Binding affinity to A*0201 was measured, $C\_1/2 \max \mu M = 6$ for 10-mer, 3 for 9-mer
- MAL variant of Pr(75-84 MN), with substitutions V77, G78, and P79, gave reduced binding and CTL recognition

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Protease(76–84) Pol( ) LVGPTPVNI HIV-1 infection human(A*0201) [Altfeld (2001d)]

- Epitope name: Pol-163. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- LVGPTPVNI binds to 4/5 HLA-A2 supertype alleles: A*0201, A*0202, A*0206 (highest affinity) and A*6802, but not A*0203
- 1/22 individuals with chronic HIV-1 infection recognized this epitope by ELISPOT
- 0/12 acutely infected individuals recognized this epitope

Protease(76–84) Pol(156–164) LVGPTPVNI HIV-1 infection human(A2 supertype) [Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)

Table 9: **Protease-RT**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Protease-RT(95–5)	Gag(175–184)	CTLNFPISPI	HIV-1 infection	human(A2 supertype)	[Propato (2001)]

- The epitope starts in Protease and ends in RT
- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)

Table 10: **RT**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
RT(1–5)	Pol(176–184)	TLNFPISPI	HIV-1 infection	human(A2 supertype)	[Propato (2001)]
	• Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes • Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs • A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus • This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)				
RT(3–12)	RT( )	SPIETVPVKL	HIV-1 infection	human(A2, B61)	[van der Burg (1997)]
	• Recognized by CTL from a long-term survivor, EILKEPVGHGV was also recognized • Highly conserved across clades				
RT(3–12)	Pol( )	SPIETVPVKL		human(B7)	[De Groot (2001)]
	• The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes • A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay • SPIETVPVKL was newly identified as HLA-B7 epitope in this study, it had been previously shown to be presented by HLA-A2 and B61				
RT(5–29)	RT(160–184 HXB2)	IETVPVKLKPGMDGP-KVKQWPLTEE	HIV-1 infection	human(B8)	[Walker (1989)]
	• One of five epitopes defined for RT-specific CTL clones in this study				
RT(18–26)	RT(185–193)	GPKVKQWPL	HIV-1 infection	human(B8)	[Oxenius (2000)]
	• Epitope name: GPK. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable • Two of the 7/8 study subjects that were HLA B8+ recognized this epitope • Patient SC2 (HLA A1, B7/8, Cw0701/0702, DR4/53, DQ7) had CTL responses against epitopes FLKEKGGL, GPKVKQWPL, and GEIYKRWII – FLKEKGGL tetramer staining steadily declined and at day 1340 the FLKEKGGL stained cells were no longer detected and the escape mutant FLKENGGI was found in 8/10 clones • Patient SC11(HLA A1, B8, Cw0201, DR3/11, DR52, DQ2/7) started therapy early, remained on therapy for 40 days, then reinitiated HAART at day 640, and had a CTL response to FLKEKGGL, GPKVKQWPL, and GEIYKRWII throughout and received a benefit from the early limited course therapy				

RT(18–26)	RT(185–193 LAI)	GPKVKQWPL		human(B*0801)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*0801 epitope					
RT(18–26)	RT(18–26)	GPKVKQWPL	HIV-1 infection	human(B8)	[Meier (1995), Menendez-Arias (1998)]
• HIV proteins with mutations in this epitope allowed transactive inhibition of specific CTL-mediated lysis • Article reviewed in [Menendez-Arias (1998)], with a discussion of antagonism					
RT(18–26)	RT(173–181)	GPKVKQWPL		human(B8)	[Goulder (1997g), Menendez-Arias (1998)]
• Included in a study of the B8 binding motif • Article reviewed in [Menendez-Arias (1998)], with a discussion of antagonism					
RT(18–26)	RT(185–193 LAI)	GPKVKQWPL		human(B8)	[Sutton (1993)]
• Predicted epitope based on B8-binding motifs, from larger peptide IETVPVKLKPGMDGPKVKQWPLTEE					
RT(18–26)	RT(185–193 LAI)	GPKVKQWPL	HIV-1 infection	human(B8)	[Klenerman (1995), Menendez-Arias (1998)]
• Naturally-occurring antagonist GPRVKQWPL found in viral PBMC DNA and RNA • Article reviewed in [Menendez-Arias (1998)] with a discussion of antagonism					
RT(18–26)	RT(18–26)	GPKVKQWPL	*in vitro* stimulation	human(B8)	[Zarling (1999)]
• This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses • Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA • A weak response to KLTPLCVSL was stimulated using macrophages as the APC • No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL					
RT(18–26)	Pol( )	GPKVKQWPL	HIV-1 infection	human(B8)	[Seth (2001)]
• CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized					
RT(18–26)	RT(185–193 SF2)	GPKVKQWPL	HIV-1 infection	human(B8)	[Altfeld (2001c)]
• Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection					

- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/3 group 2, and 2/2 group 3

RT(18–26)	Pol(171–180)	GPKVKQWPL	HIV-1 exposed seronegative, HIV-1 infection	human(B8)	[Kaul (2001a)]

- GPKVKQWPL is cross-reactive for clades A, B, C, and D
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

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RT(18–26)	RT(18–26)	GPKVKQWPL	HIV-1 infection	human(B8)	[Day (2001)]

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual

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RT(18–27)	Pol( )	GPKVKQWPLT		human(B7,B8)	[De Groot (2001)]

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay
- GPKVKQWPLT was confirmed as a previously identified HLA-B8 epitope, and newly identified as an HLA-B7 epitope in this study

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RT(33–41)	RT(33–41 LAI)	ALVEICTEM	HIV-1 infection	human(A*0201)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*0201 epitope

RT(33–41)	RT(33–41 LAI)	ALVEICTEL	HIV-1 infection	human(A*0201)	[Samri (2000)]

- This epitope contains the mutation M41L, a mutation induced by nucleoside reverse transcriptase inhibitors
- Patient 201#5, (A*0201), was found by ELISPOT to recognize the mutated peptide after zidovudine treatment, but not the wild-type peptide – the mutation M41L gave an increased A2 binding score (http://bimas.dcrt.nih.gov/molbio/hla_bind) compared to the wildtype RT sequence
- Three additional A*0201 individuals and one B27 individual did not respond to this epitope before or after treatment
- M41L occurred at anchor positions p2 and p9 in several computer predicted RT epitopes (33-41, 32-41, and 40-49) (http//bimas.dcrt.nih.gov/molbio/hla_bind), and increased the predicted binding affinity for 6 HLA molecules (B*2705, B5102, C3, A0201, B*2705 and B3901)

RT(33–41)	RT(33–41)	ALVEICTEM	HIV-1 infection	human(A2)	[Haas (1998)]

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules

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RT(33–41)	RT(33–41)	ALVEICTEM	HIV-1 infection	human(A2)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- SLYNTVATL was the dominant A2 epitope recognized in patients with chronic infection, except for Subject 11841 who recognized 5/8 epitopes and who had a dominant A-2 response to ALVEICTEM

RT(33–43)	RT(33–43)	ALVEICTEMEK	HIV-1 infection	human(A*0301)	[Haas (1998)]

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules
- C. Brander notes that this is an A*0301 epitope in the 1999 database, G. Haas pers. comm.

RT(33–43)	RT(33–43)	ALVEICTEMEK	HIV-1 infection	human(A*0301)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*0301 epitope

RT(33–43)	RT(33–43)	ALVEICTEMEK	HIV-1 infection	human(A3)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant

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RT(38–52)	RT(203–209)	CTEMEKEGKISKIGP	Vaccine	murine(H-2^d)	[Burnett (2000)]

Vaccine: *Vector/type:* Salmonella *HIV component:* RT epitope

- A live attenuated bacterial vaccine, Salmonella SL3261-pHART, with an inserted HIV epitope in the Lpp-OmpA-HIV fusion protein, induced a specific CTL response in BALB/c mice (<15% lysis assayed by Cr-release of target cells)

RT(38–52)	RT(205–219 BRU)	CTEMEKEGKISKIGP	Vaccine	murine(H2^k)	[De Groot (1991), Menendez-Arias (1998)]

Vaccine: *Vector/type:* recombinant protein *Strain:* BRU *HIV component:* RT

- Murine and human helper and CTL epitope
- Epitope noted in a review by [Menendez-Arias (1998)] to be located in the “fingers” domain of RT and is a helper and CTL epitope

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RT(38–52)	RT(205–219)	CTEMEKEGKISKIGP	HIV-1 infection	human(broad)	[Hosmalin (1990), Menendez-Arias (1998)]

- Murine and human helper and CTL epitope
- Epitope noted in a review by [Menendez-Arias (1998)] to be located in the "fingers" domain of RT and is a helper and CTL epitope

RT(39–47)	RT(206–214)	TEMEAEGKI	*in vitro* stimulation	C3H/HeJ mice( )	[Leggatt (1997)]

- Ala-substituted nonamer-peptide used to test a non-radioactive assay for murine CTL recognition of peptide-MHC class I complexes
- The new assay is CTL adherence assay (CAA), and is based on the discovery that CTL develop adhesive properties upon TCR triggering
- Substitutions in TEMEAEGKI that reduce cytolytic activity were correctly detected by CAA

RT(39–47)	RT( )	TEMEKEGKI		murine(H-2K^k)	[Leggatt (1998)]

- Epitope variants were examined for CTL response in concert with H-2K^k MHC class I binding – all of the following combinations were observed: (i) two single mutations which did not alone abrogate CTL activity did abrogate activity when combined, (ii) loss of recognition of a single substitution could be restored by an additional substitution, and (iii) sometimes there was recognition of two single substitutions as well as the combination of those substitutions
- 2E and 9I are anchor residues for H-2K^k – if you have M in the third position, it enhances H-2K^k binding 10-fold, but polymorphism at this site is important for the overall conformation of the peptide and can influence T-cell recognition

RT(42–50)	RT(42–50 LAI)	EKEGKISKI	HIV-1 infection	human(B*5101)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*5101 epitope

RT(42–50)	RT(42–50 LAI)	EKEGKISKI	HIV-1 infection	human(B51)	[Haas (1998)]

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules

RT(57–65)	Pol(236–244)	NTPVFAIKK	HIV-1 infection	human(A3 supertype)	[Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

RT(73–82)	RT(73–82 LAI)	KLVDFRELNK	HIV-1 infection	human(A3)	[Samri (2000)]

- This epitope contains the mutation L74V, a frequent mutation induced by nucleoside reverse transcriptase inhibitors
- The wild-type, but not the mutated peptide, was recognized before and after zidovudine treatment in A3-restricted patients 252#0 and 252#4
- Mutation L74V affects the p2 anchor position in RT epitopes and was predicted to reduce binding to A3 (http://bimas.dcrt.nih.gov/molbio/hla_bind)

RT(93–101)	( )	GIPHPAGLK		(A3)	[Altfeld(2000), Brander & Goulder(2001)]
RT(93–102)	Pol(240–249 93TH253 CRF01)	GIPHPAGLKK	HIV-1 exposed seronegative	human(A11)	[Sriwanthana (2001)]

- Epitope name: P248-257. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was weakly reactive in the HEPS study subject 265 who was HLA A2/A11 and after a second stimulation *in vitro* gave a strong response in HEPS study subject 128 who was HLA A11/A33

RT(93–102)	Pol(240–249 93TH253 CRF01)	GIPHPAGLKK	HIV-1 infection	human(A11)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it
- This epitope was highly conserved in other subtypes, and exact matches were common

RT(98–113)	RT(252–266)	AGLKKKKSVTVLDVG-D	HIV-1 infection	human(Cw4)	[Bernard (1998)]

- This study focuses on six rare HIV-infected long-term survivors who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs

RT(103–117)	RT(257–251)	KKSVTVLDVGDAYFS	HIV-1 infection	human(Cw4)	[Bernard (1998)]

- This study focuses on six rare HIV-infected long-term survivors who were infected for many years without exhibiting immune
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs

RT(107–115)	RT(262–270 IIIB)	TVLDVGDAY		(B*3501)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*3501 epitope

RT(107–115)	RT(262–270 IIIB)	TVLDVGDAY	HIV-1 infection	human(B35)	[Menendez-Arias (1998), Wilson (1996)]

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study
- TVLDMGDAC is a naturally occurring variant that is less reactive
- [Menendez-Arias (1998)], in a review, notes that this epitope includes a catalytic residue (Asp-110) in the active site of RT

RT(107–115)	Pol(262–270 IIIB)	TVLDVGDAY	HIV-1 infection	human(B35)	[Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- An additional variant that gave a positive CTL response: TVLDMGDAC

RT(107–115)	Pol(262–270)	TVLDVGDAY	HIV-1 infection	human(B35)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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RT(107–115)	RT(262–270 SF2)	TVLDVGDAY	HIV-1 infection	human(B35)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 0/1 group 3

RT(108–118)	RT(267–277)	VLDVGDAYFSV	*in vitro* stimulation	human(A*0201)	[van der Burg (1996)]

- High dissociation rate, but immunogenic in primary CTL induction after repeated stimulations with peptide
- CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual

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RT(108–118)	RT(267–277)	VLDVGDAYFSV	HIV-1 infection	human(A2)	[Kundu (1998b)]

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated
- VLDVGDAYFSV is a conserved HLA-A2 epitope included in this study – 4/6 patients had this sequence as their HIV direct sequence, but only one of these had a detectable CTL response – the other two had the sequences EEDVGDAYFSV and ELDVGDAYFSV and no detectable CTL response

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RT(108–118)	RT(267–277)	VLDVGDAYFSV	*in vitro* stimulation	human(A2)	[van der Burg (1995)]

- Binds HLA-A*0201 – CTL generated by *in vitro* stimulation of PBMC from an HIV negative donor
- VLDVGDAYFSV is in a functional domain

RT(108–118)	Pol(263–273)	VLDVGDAYFSV	HIV-1 infection	human(A2, A*0201)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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RT(108–122)	RT(257–251)	VLDVGDAYFSVPLDE	HIV-1 infection	human(Cw4)	[Bernard (1998)]

- This study focuses on six rare HIV-infected long-term survivors who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs

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RT(113–120)	Pol(268–275 SF2)	DAYFSVPL	HIV-1 infection	human(B*5101, B24)	[Tomiyama (1999)]

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA -B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed
- Four of the six epitopes were highly conserved among B subtype sequences, DAYFSVPL is conserved

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RT(117–126)	Pol(264–273 93TH253 CRF01)	SVPLDESFRK	HIV-1 exposed seronegative	human(A11)	[Sriwanthana (2001)]

- Epitope name: P272-281. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope after a second stimulation *in vitro* gave a strong response in HEPS study subject 128 who was HLA A11/A33

RT(117–126)	Pol(264–273 93TH253 CRF01)	SVPLDESFRK	HIV-1 infection	human(A11)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 3/8 tested FSWs recognized it
- This epitope was only conserved in CRF01, and subtype A and B, and exact matches were uncommon

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RT(118–126)	Pol(273–282)	VPLDKDFRKY	HIV-1 infection	human(B*3501)	[Tomiyama (2000a)]

- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

RT(118–126)	( )	VPLDEDFRKY	HIV-1 infection	human(B*3501)	[Tomiyama (2000b)]

- Epitope name: HIV-B3501-SF2-4. B*3501-VPLDEDFRKY tetramer binding did not inhibit CTL activity of a clone that reacts with both HLA-B*3501 and HLA-B*5101 presentation of the epitope IPLTEEAEL

RT(118–126)	RT(273–282 SF2)	VPLDEDFRKY	HIV-1 infection	human(B35)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 1/1 group 3

RT(118–127)	RT(273–282 SF2)	VPLDKDFRKY	HIV-1 infection	human(B*3501)	[Menendez-Arias (1998), Tomiyama (1997)]

- A CTL clone responsive to this epitope was obtained
- 4/7 B35-positive individuals had a CTL response to this epitope
- A K to E substitution at position 5 abrogates specific lysis, and reduces binding to B*3501
- [Menendez-Arias (1998)], in a review, notes that a Glu to Lys (E to K) change abrogates CTL activity, but that both VPLDEDFRKY and VPLDKDFRKY can serve as HLA-B35 epitopes, so the change must alter T-cell receptor binding – residues in this epitope may be important for polymerase activity

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RT(118–127)	RT(273–282 IIIB)	VPLDEDFRKY	HIV-1 infection	human(B*3501)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*3501 epitope

RT(118–127)	RT(273–282 IIIB)	VPLDEDFRKY	HIV-1 infection	human(B*3501,B35)	[Shiga (1996)]

- Binds HLA-B*3501

RT(118–127)	( )	VPLDKDFRKY	HIV-1 infection	human(B35)	[Kawana (1999)]

- HLA B35 is associated with rapid disease progression
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals – only one of these reduced the binding of the peptide to B35 and was shown to be an escape mutation
- `-----E----` was found in 8/10 of the B35+ individuals, and three of the B35- individuals – the D –> E substituted peptide had similar binding affinity to B35 and was equally susceptible to a CTL clone

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RT(118–127)	RT(273–282 IIIB)	VPLDEDFRKY	HIV-1 infection	human(B35)	[Sipsas (1997)]

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by three lab workers accidentally infected with HIV-1 IIIB

- VPLDKDFRKY, a variant found in HIV MN, was not recognized
- VPHDEDFRKY, a variant found in HIV YU2, was not recognized
- This epitope was type-specific and conserved in only one other B subtype sequence

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RT(126–135) RT(293–302 HXB) KYTAFTIPSI HIV-1 infection human(A2) [Shankar (1998)]

- A novel CTL clone was defined with a panel of recombinant vaccinia-RT-infected B-LCL target cells using PBMCs donated by a patient who was HIV-seropositive for 6 years and had not received any antiretroviral therapy
- There is evidence that some CTL epitopes are poorly presented on the surface of infected cells, but this RT epitope was recognized as effectively on HIV-infected cells as on peptide-pulsed targets

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RT(127–135) Pol( ) YTAFTIPSI HIV-1 infection human(A2) [Altfeld (2001d)]

- Epitope name: Pol-316. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- 2/22 individuals with chronic HIV-1 infection recognized this epitope in ELISPOT
- 0/12 acutely infected individuals recognized this epitope
- YTAFTIPSI binds to five HLA-A2 supertype alleles: A*0201, A*0202, A*0203, A*0206 and A*6802 (highest affinity)

RT(127–135) Pol(306–314) YTAFTIPSI HIV-1 infection human(A2 supertype) [Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)

RT(128–135) Pol(283–290 HXB2) TAFTIPSI HIV-1 infection human(A*0217) [Mulligan (2001)]

- Epitope P28 from Patient 12129 with HLA genotypes A*0207, A*0217, B*0801, B*4002, Cw*0303, Cw*07(01, 06)

RT(128–135) RT(295–302 IIIB) TAFTIPSI HIV-1 infection human(B*5101) [Brander & Goulder(2001)]

- C. Brander notes this is a B*5101 epitope

RT(128–135) Pol(283–290 SF2) TAFTIPSI HIV-1 infection human(B*5101) [Tomiyama (1999)]

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%

- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed
- Four of the six epitopes were highly conserved among B subtype sequences, but TAFTIPSI is somewhat variable

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RT(128–135) RT(295–302) TAFTIPSI HIV-1 infection human(B*5101) [Samri (2000)]

- Epitope name: P5. The epitope TAFTIPSI was recognized by patient 246#1 in a study of the effects of therapy escape mutations on CTL recognition

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RT(128–135) RT(295–302 IIIB) TAFTIPSI HIV-1 infection human(B51) [Menendez-Arias (1998), Sipsas (1997)]

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB
- TAFTIPST, a variant found in HIV-1 CAM1, was also recognized but 100-fold more peptide was needed
- TAFTIPSV, a variant found in HIV-1 VE1RT, was also recognized, but 10-fold more peptide was needed
- TVFTIPSI, a variant found in HIV-1 MANC, was also recognized
- [Menendez-Arias (1998)], in a review, notes that this epitope includes a region near the active site of RT – the substitution of the position two conservative change from A to V decreases CTL recognition

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RT(128–135) RT(295–302) TAFTIPSI HIV-1 infection human(B51) [Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- Three of the four individuals that responded to SLYNTVATL recognized additional HIV epitopes, and all three were also HLA B51 and recognized this epitope as well as other epitopes

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RT(128–135) RT(295–302) TAFTIPSI HIV-1 infection human(B51) [Oxenius (2000)]

- Epitope name: TAF. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- None of the 8 study subjects recognized this epitope but none were HLA B51+

RT(128–135) RT(295–302 LAI) TAFTIPSI HIV-1 infection human(B51) [Mollet (2000)]

- Epitope name: P5. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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RT(151–159) Pol(306–314 SF2) QGWKGSPAI HIV-1 infection human(B*5101) [Tomiyama (1999)]

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS

- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed
- Four of the six epitopes were highly conserved among B subtype sequences, QGWKGSPAI is conserved

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RT(153–165) RT(308–320) WKGSPAIFQSSMT HIV-1 infection human(B7) [Brander & Walker(1995)]

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study

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RT(153–165) Pol(308–320) WKGPAIFQSSMT HIV-1 infection human(B7) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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RT(153–167) RT( ) WKGSPAIFQSSMTKI HIV-1 infection human( ) [Altfeld (2001a)]

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses is underestimated if accessory proteins are not included in the study
- RT peptides SQIYPGIKVRQLCKL and WKGSPAIFQSSMTKI were recognized

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RT(156–164) RT(311–319 SF2) SPAIFQSSM HIV-1 infection human(B*3501) [Menendez-Arias (1998), Tomiyama (1997)]

- A CTL clone responsive to this epitope was obtained
- Only 1/7 B35-positive individuals had a CTL response to this epitope
- [Menendez-Arias (1998)], in a review, notes that this epitope is near the active site of RT

RT(156–164) RT(311–319 SF2) SPAIFQSSM HIV-1 infection human(B35) [Menendez-Arias (1998), Shiga (1996)]

- Binds HLA-B*3501
- [Menendez-Arias (1998)], in a review, notes that this epitope includes catalytic residues in the active site of RT

RT(156–164) Pol(311–319) SPAIFQSSM HIV-1 infection human(B35) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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RT(156–164) Pol(156–164 HXB2) SPAIFQSSM HIV-1 infection human(B7) [Hay (1999)]

- CTL response to IPRRIRQGL was the immunodominant response in a rapid progressor – there was a subdominant response to SPAIFQSSM in Pol, and interestingly, no response to commonly immunodominant HLA A*0201 epitope SLYNTVATL, although this individual was HLA A*0201
- The individual showed a strong initial CTL response at the time of the initial drop in viremia, but it was quickly lost, although memory cells persisted
- Despite the initial narrow response to two epitopes, no other CTL responses developed

- No HIV-specific lymphoproliferative responses were detected in this patient, and neutralizing antibody response was weak
- Variants of this epitope were observed *in vivo* (`------C--`, `--S------`), but the binding motifs for B7 were preserved (P2, and C-term aromatic or hydrophobic)

RT(156–164) Pol( ) SPAIFQSSM HIV-1 infection human(B7) [Islam (2001)]

- Subject 053i was followed longitudinally from acute infection through death, and had rapid progression to AIDS
- This individual had a dominant response to IPRRIRQGL with strong *in vivo* activated responses and *in vitro* stimulated memory responses and a subdominant response to SPAIFQSSM – during the course of disease progression (4 Years), the functional CTL responses were lost and no sequence variation occurred within both epitopes, but CTL clones specific for IPRRIRQGL persisted throughout

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RT(156–164) RT(323–331 SF2) SPAIFQSSM HIV-1 infection human(B7) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3

RT(156–165) RT(311–319 LAI) SPAIFQSSMT HIV-1 infection human(B35) [Samri (2000)]

- Epitope name: P4. This epitope contains the mutation P157S which can be induced by nucleoside reverse transcriptase inhibitors
- It was recognized by patient 252#0 in a study of the effects of therapy escape mutations on CTL recognition

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RT(156–165) RT(311–319 SF2) SPAIFQSSMT human(B7) [Brander & Walker(1997), Menendez-Arias (1998)]

- Pers. Comm. from C. Hey and D. Ruhl to C. Brander and B. Walker
- [Menendez-Arias (1998)], in a review, notes that this epitope includes catalytic residues in the active site of RT

RT(156–165) RT(311–319 SF2) SPAIFQSSMT HIV-1 infection human(B7) [Mollet (2000)]

- Epitope name: P4. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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RT(156–165) Pol( ) SPAIFQSSMT human(B7) [De Groot (2001)]

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes

- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay
- SPAIFQSSMT was confirmed as a previously identified HLA-B7 epitope in this study

RT(158–166)	RT(325–333 LAI)	AIFQSSMTK	HIV-1 infection	human(A*0301)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*0301 epitope

RT(158–166)	RT(325–333 LAI)	AIFQSSMTK	HIV-1 infection	human(A*1101)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*1101 epitope

RT(158–166)	RT(325–333)	AIFQSSMTK	HIV-1 infection	human(A*1101, A3, A*0301, A*6801)	[Menendez-Arias (1998), Threlkeld (1997)]

- Study of the fine specificity of an A3-like super-type epitope (the A3 super-type includes A*0301, A*1101, A*3101, A*3301, and A*6801)
- A3 super-type is characterized by a hydrophobic or hydroxyl containing anchor residue at position 2, and a positive charge in the C-term position
- While most lines were specific, promiscuous cloned CTL lines were also derived from HIV+ donors that could recognize epitope presented by either A3 or A11 or A*6801
- Alanine substitutions throughout the epitope and natural variants indicate that the same amino acid positions are critical for presentation by either MHC molecule, A3 or A11
- AIFQSSMTK is presented by three members of the A3 superfamily: A*0301, A*1101, and A*6801, and the naturally occurring variants A1S and K9R are recognized with similar efficiency to wild type epitope – AIFQRSMTR can also bind to two additional members of the A3 superfamily, A*3101 and A*3301

RT(158–166)	RT( )	AIFQSSMTK	HIV-1 infection	human(A11)	[Wagner (1998a)]

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1 α and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules

RT(158–166)	RT(325–333 LAI)	AIFQSSMTK	Peptide-HLA interaction	human(A11)	[Menendez-Arias (1998), Zhang (1993)]

- Exploration of A11 binding motif, based on Nixon *et al.* 1991

RT(158–166)	RT(325–333 LAI)	AIFQSSMTK	HIV-1 infection	human(A11)	[McMichael & Walker(1994)]

- Review of HIV CTL epitopes

RT(158–166)	Pol(305–313 93TH253 CRF01)	AIFQSSMTK	HIV-1 exposed seronegative, HIV-1 infection	human(A11)	[Sriwanthana (2001)]

- Epitope name: P313-321. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand

- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was weakly reactive in the HEPS study subject 128 who was HLA A11/A33
- This epitope was strongly reactive in HIV+ study subjects 053 and 184 who carried HLA-A11

RT(158–166) Pol(305–313 93TH253 CRF01) AIFQSSMTK HIV-1 infection human(A11) [Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined
- 6/8 tested FSWs recognized this epitope
- An HLA-A11 tetramer was made for this epitope, which was recognized by two subjects – and both subjects had expanded tetramer staining T-cell populations after *in vitro* stimulation
- This epitope was highly conserved in other subtypes, and exact matches were common

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RT(158–166) RT(325–333 IIIB) AIFQSSMTK HIV-1 infection human(A3) [Wilson (1996)]

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study
- AIFQSSMTR and AILQSSMTK, naturally occurring variants, were found in the infant, and are recognized
- TISQSSMTK, a naturally occurring variant, was found in the infant and is not recognized

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RT(158–166) RT(325–333 LAI) AIFQSSMTK HIV-1 infection human(A3) [Cao (1997)]

- The consensus peptide of B and D clade viruses is AIFQSSMTK
- The consensus peptide of a subset of As is AIFQASMTK and it is less able to stimulate the CTL clone
- The consensus peptide of a subset of As is SIFQSSMTK and is as reactive as the originally defined epitope

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RT(158–166) Pol(325–333 IIIB) AIFQSSMTK HIV-1 infection human(A3) [Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- One variant found in an infant gave a positive CTL response: AIFQSSMTR
- AIFLSSMTK and TISQSSMTK were escape mutants

RT(158–166) RT(325–333 SF2) AIFQSSMTK HIV-1 infection human(A3) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection

- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 0/7 group 1, 0/4 group 2, and 1/2 group 3

RT(158–166) RT(158–166) AIFQSSMTK HIV-1 infection human(A3) [Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant
- In two of the subjects, AIFQSSMTK was the dominant epitope

RT(158–166) Pol(337–345) AIFQSSMTK HIV-1 infection human(A3 supertype) [Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

RT(158–166) Pol(313–321) AIFQSSMTK HIV-1 infection human(A3, A11) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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RT(158–166) RT(325–333) AIFQSSMTK HIV-1 infection human(A3.1) [Brander & Walker(1995)]

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study

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RT(158–166) RT(325–333) AIFQSSMTK HIV-1 infection human(A3.1) [Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- 1/11 of the A2+ individuals was HLA A3 and reacted with this epitope as well as two other A3.1 epitopes

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RT(158–166) RT(325–333 LAI) AIFQSSMTK human(A33) [Rowland-Jones(1995)]

- Defined as minimal peptide by titration curve, S. Rowland-Jones, Pers. Comm.

RT(158–166)	( )	AIFQSSMTK	HIV-1 infection	human(A33)	[Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized in 1/22 HEPS sex worker controls, ML1668

RT(158–166)	RT(325–333 LAI)	AIFQSSMTK	HIV-1 infection	human(A3supertype)	[Mollet (2000)]

- Epitope name: P3. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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RT(158–166)	( )	AIFQSSMTK	HIV-1 infection	human(B*0301)	[Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

RT(158–166)	Pol(325–333)	AIFQSSMTK	HIV-1 exposed seronegative, HIV-1 infection	human(A3, A11, A33)	[Kaul (2001a)]

- Variants (S/A)IFQSSMTK are specific for the A/B clades
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women

- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-A3 women, 2/2 HEPS and 3/3 HIV-1-infected women recognized this epitope
- The dominant response to this HLA allele was to this epitope in one of the 2/2 HEPS cases and in one of the 3/3 HIV-1-infected women

RT(158–182)	RT(325–349 PV22)	AIFQSSMTKILEPFRKQ-NPDIVIYQ	HIV-1 infection	human(A11)	[Jassoy (1993)]

- HIV-1 specific CTLs release γ-IFN, and α- and β-TNF

RT(158–182)	RT(325–349)	AIFQSSMTKILEPFRKQ-NPDIVIYQ	HIV-1 infection	human(A11)	[Price (1995)]

- Study of cytokines released by HIV-1 specific activated CTL

RT(164–172)	Pol(343–351)	MTKILEPFR	HIV-1 infection	human(A3 supertype)	[Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 4/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

RT(173–181)	RT(173–181 LAI)	KQNPDIVIY		human(A*3002)	[Brander & Goulder(2001), Goulder (2001b)]

- C. Brander notes this is an A*3002 epitope

RT(173–181)	RT( )	KQNPDIVIY	HIV-1 infection	human(A*3002)	[Goulder (2001a)]

- Epitope name: KY9 (RT-53). HLA-A*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule
- A rapid method was developed combining ELISPOT with intracellular IFN-γ staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood
- Two individuals were studied: Subject 199 (HLA A*0201/*3002 B*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A*3002/ B53/*5801 Cw4/7) an African-Caribbean
- In both HLA-A*3002 individuals the response to RSLYNTVATLY was dominant
- In subject 199 four additional A*3002 epitopes were identified
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)

RT(175–183)	Pol( )	HPDIVIYQY	HIV-1 infection	human(B35)	[Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- HPDIVIYQY or NPDIVIYQY was recognized in 1 of the 6 women (ML857), and the response was present in the last available sample prior to seroconversion, 7 months
- 20/20 sequences of the infecting strain had three substitutions in this epitope, all 20 were NpQiIiyqy, and this form was not recognized by CTL from ML 857 – this was the only case in the study where a virus carrying an unrecognized form of the epitope broke through
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- NPDIVIYQY was recognized by 1/22 HEPS control sex workers, ML887

RT(175–183) RT(328–336 IIIB) NPDIVIYQY HIV-1 infection human(B*3501) [Tomiyama (1997)]

- A CTL clone responsive to this epitope was obtained
- 3/7 B35-positive individuals had a CTL response to this epitope
- D to E, or V to I, substitutions at positions 3 or 5, respectively, reduces CTL activity and binding to B*3501

RT(175–183) RT(328–336 IIIB) NPDIVIYQY HIV-1 infection human(B*3501) [Brander & Goulder(2001)]

- C. Brander notes this is a B*3501 epitope

RT(175–183) RT(342–350 LAI) HPDIVIYQY HIV-1 infection human(B*3501) [Brander & Goulder(2001)]

- C. Brander notes this is a B*3501 epitope

RT(175–183) Pol(330–338) NPDIVIYQY HIV-1 infection human(B*3501) [Tomiyama (2000a)]

- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

RT(175–183) RT(342–350 LAI) HPDIVIYQY HIV-1 infection human(B35) [McMichael & Walker(1994)]

- Review of HIV CTL epitopes

RT(175–183) RT(329–337) HPDIVIYQY HIV-1 infection human(B35) [Rowland-Jones (1995)]

- NPDIVIYQY preferred sequence for some CTL clones, HIV-2 NPDVILIQY is also recognized

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RT(175–183) ( ) NPDIVIYQY HIV-1 infection human(B35) [Kawana (1999)]

- HLA B35 is associated with rapid disease progression
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals

- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals – only one of these reduced the binding of the peptide to B35 and was shown to be an escape mutation
- `--E------` was found in 8/10 of the B35+ individuals, and two of the B35- individuals – the D –> E substituted peptide had reduced binding affinity to B35 and may be an escape mutant

RT(175–183)	RT(329–337)	HPDIVIYQY	*in vitro* stimulation	human(B35)	[Lalvani (1997)]

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors

RT(175–183)	RT(328–336 IIIB)	NPDIVIYQY	HIV-1 infection	human(B35)	[Menendez-Arias (1998), Shiga (1996)]

- Binds HLA-B*3501
- CTL activity to this epitope was originally detected in a long-term survivor, however it has since been found in normal progressors – it is cross-reactive with HIV-2 (HPDILIYQY), but D3E and V5I substitutions reduce binding [Menendez-Arias (1998)]

RT(175–183)	RT(328–336 IIIB)	NPDIVIYQY	HIV-1 infection	human(B35)	[Menendez-Arias (1998), Sipsas (1997)]

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB
- NPDIIIYQY, a variant found in HIV-1 JRCSF, was also recognized
- NPEIVIYQY, was also recognized
- NPDLVIYQY, was also recognized
- [Menendez-Arias (1998)], in a review, notes that the YXDD motif, highly conserved among polymerases, overlaps this epitope – CTL activity to this epitope was originally detected in a long-term survivor, however it has since been found in normal progressors – it is cross-reactive with HIV-2 (HPDILIYQY), but D3E and V5I substitutions reduce binding

RT(175–183)	RT( )	NPDIVIYQY	HIV-1 exposed seronegative	human(B35)	[Menendez-Arias (1998), Rowland-Jones (1998a)]

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating
- The A subtype consensus is HPDIVIYQY
- The D subtype consensus is NPEIVIYQY
- [Menendez-Arias (1998)], in a review, notes that the YXDD motif, highly conserved among polymerases, overlaps this epitope – CTL activity to this epitope was originally detected in a long-term survivor, however it has since been found in normal progressors – it is cross-reactive with HIV-2 (HPDILIYQY), but D3E and V5I substitutions reduce binding

RT(175–183)	Pol( )	NPDIVIYQY	HIV-1 exposed seronegative	human(B35)	[Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- Clade A version of epitope HPDIVIYQY, clade D NPEIVIYQY

RT(175–183) Pol( ) HPDIVIYQY human(B35) [Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective
- HIV-2 version of this epitope is not conserved: NPDVILIQY, but the CTLs are cross-reactive – one of five B35 CTL epitopes that are cross-reactive, see also [Rowland-Jones (1995)]

RT(175–183) ( ) HPDIVIYQY HIV-1 infection human(B35) [Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

RT(175–183) Pol(342–350) HPDIVIYQY HIV-1 exposed seronegative, HIV-1 infection human(B35) [Kaul (2001a)]

- Variants (H/N)PDIVIYQY are specific for the A/B clades
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B35 women, 2/3 HEPS and 1/4 HIV-1-infected women recognized this epitope

- The dominant response to this HLA allele was to this epitope in only one of the 2/3 HEPS cases, and was not to this epitope in the one responsive HIV-1-infected women
- Subject ML 857 shifted from an A*6802 DTVLEDINL and B35 H/NPDIVIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion and the loss of the pre-seroconversion response was not due to sequence variation within these epitopes

RT(175–184)	RT(175–184 LAI)	NPDIVIYQYM	HIV-1 infection	human(B51)	[Samri (2000)]

- This epitope contains the mutation M184V, a frequent mutation induced by nucleoside reverse transcriptase inhibitors
- Patient 246#1 (B51), was found by ELISPOT to recognize the wild type and the mutated peptide after zidovudine treatment
- The resistance mutation M184V gave an increased predicted binding score to B51 (http://bimas.dcrt.nih.gov/molbio/hla_bind) compared to the wildtype RT sequence and also an increased ELISPOT reactivity

RT(175–199)	RT(342–366 LAI)	NPDIVIYQYMDDLYV-GSDLEIGQHR	HIV-1 infection	human(A11)	[Menendez-Arias (1998), Walker (1989)]

- One of five epitopes defined for RT-specific CTL clones in this study

RT(179–187)	RT( )	VIYQYMDDL	Vaccine	human(A*0201)	[Hanke (1998a), Hanke (1998b)]

Vaccine: *Vector/type:* vaccinia *HIV component:* polyepitope

- This epitope was shown to be processed and presented to appropriate CTL clones upon infection of human target cells with vaccinia virus Ankara (VVA) carrying 20 HIV-1 epitopes recognized by humans

RT(179–187)	RT( )	VIYQYMDDL	HIV-1 infection	human(A*0201)	[Tan (1999)]

- Adoptive transfer of two autologous *in vitro*-expanded CTL clones against the A*0201 restricted epitopes SLYNTVATL and VIYQYMDDL were infused into a patient – they were well tolerated, but the SLYNTVATL clone was shown by tetramer staining to be rapidly eliminated through apoptosis, and the treatment had no impact upon viral load and CD4 and CD8 cell counts
- Tetramer staining failed for the VIYQYMDDL epitope as the tetramer was unstable

RT(179–187)	Pol(346–354)	VIYQYMDDL	HIV-1 infection	human(A*0201)	[Sewell (1999)]

- Proteasome regulation influences epitope processing and could influence patterns of immunodominance
- The proteasome is inhibited by lactacystin treatment, and γ IFN induces expression of proteasome subunits, LMP2 and LMP7, which combine with the proteasome to create an immunoproteasome
- IFN-γ induction of the immunoproteasome and lactacystin inhibition increases the presentation of the A*0201 VIYQYMDDL epitope, but decreases the presentation of the A*0201 ILKEPVHGV epitope, which is immunodominant within pol proteins, showing the two epitopes are processed by different pathways
- ILKEPVHGV seems to be processed by the classical proteasome pathway, while VIYQYMDDL appears to be destroyed by this pathway
- This epitope contains the catalytic site (YMDD) of RT, a conserved sequence in HIV-1 which restricts escape mutants

RT(179–187)	RT(346–354 LAI)	VIYQYMDDL	HIV-1 infection	human(A*0201)	[Harrer (1996a), Menendez-Arias (1998)]

- The substitution VIYQYVDDL abrogates CTL response and confers drug resistance
- [Menendez-Arias (1998)], in a review, notes that this epitope includes catalytic residues (Asp-185 and Asp-186) in the active site of RT

RT(179–187)	RT(346–354 LAI)	VIYQYMDDL	HIV-1 infection	human(A*0201)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*0201 epitope

RT(179–187)	RT(346–354)	VIYQYMDDL	HIV-1 infection	human(A*0201)	[Brander (1998), Menendez-Arias (1998)]

- Of 17 infected HLA A*0201 subjects, 13 had CTL responses against the p17 SLYNTVATL epitope, six recognized ILKEPVHGV and five recognized VIYQYMDDL, and there was no correlation between viral load and recognition of a specific epitope or evidence of immune escape
- Only one subject had CTL against all three epitopes
- Subjects were part of the San Francisco City Clinic Cohort, the ARIEL project and from the Boston area
- In the review [Menendez-Arias (1998)] the authors note that substitution of three residues in this epitope can confer resistance to RT inhibitors (1, 3, and 6) – substitutions V1E and M6V abolish CTL activity, and M6V confers resistance to 3TC – substitution Y3C reduces CTL activity and is associated with resistance to non-nucleoside RT inhibitors

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RT(179–187)	RT( )	VIYQYMDDL	HIV-1 infection	human(A*0201)	[Altfeld (2001d)]

- Epitope name: RT VL9. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, including RT VL9, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- RT VL9 was not recognized by any of the 22 HLA-A2 patients with chronic HIV-1 infection or the 13 HLA-A2 patients with acute HIV-1 infection included in this study

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RT(179–187)	RT(346–354)	VIYQYMDDL	HIV-1 infection	human(A*0201)	[Dela Cruz (2000)]

- Epitope name: VL9. Integration of HIV RT CTL epitopes into the N-terminus of the HLA-A2 heavy chain, or tethering the epitopes to the target chain, resulted in epitope-specific lysis by CD8+ CTL
- These antigens could also be used to stimulate primary responses *in vitro*

RT(179–187)	RT( )	VIYQYMMDL	HIV-1 exposed seronegative	human(A2)	[Rowland-Jones (1998a)]

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating
- The A and D consensus sequences are both VIYQYMMDL

RT(179–187) Pol(346–354) VIYQYMDDL Vaccine human(A2) [Woodberry (1999)]

Vaccine: *Vector/type:* DNA prime with vaccinia boost *HIV component:* polyepitope

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested
- VIYQYMDDL was recognized by 3 of the HLA-A2 patients

RT(179–187) RT(179–187) VIYQYMDDL HIV-1 infection human(A2) [Schmitt (2000)]

- The mutation M184V confers resistance to lamivudine, and is in the middle of the HLA-A2 epitope VIYQYMDDL
- 1/28 individuals tested produced HIV-1 RT-specific CTL that recognized the peptide representing the lamivudine escape mutants VIYQYVDDL and VIYQYIDDL, but failed to recognize the wildtype epitope VIYQYMDDL
- This suggests immunotherapy stimulating anti-VIYQYVDDL responses may be helpful for reducing lamivudine escape

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RT(179–187) RT(179–187) VIYQYMDDL HIV-1 infection human(A2) [Haas (1998)]

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)

RT(179–187) Pol(339–347 93TH253 CRF01) VIYQYMDDL HIV-1 infection human(A2) [Sriwanthana (2001)]

- Epitope name: P334-342. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2

RT(179–187) Pol(339–347 93TH253 CRF01) VIYQYMDDL HIV-1 infection human(A2) [Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested
- 2/4 tested FSWs recognized the E clade version of this epitope, which is identical to the previously defined B clade version VIYQYMDDL

	• This epitope was conserved in many subtypes, and exact matches were very uncommon				
RT(179–187)	RT(179–187)	VIYQYMDDL	HIV-1 infection	human(A2)	[Day (2001)]
	• The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP) • Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person				
RT(179–187)	Pol( )	VIYQYMMDL	HIV-1 exposed seronegative	human(A2, A*0202)	[Rowland-Jones (1998b)]
	• HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection • Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world • Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes • This epitope is conserved among A, B and D clade viruses				
RT(180–189)	RT( )	IYQYMDDLYV	HIV-1 infection	human(A*0201)	[Menendez-Arias (1998), van der Burg (1997)]
	• Recognized by CTL from a progressor, spans important RT functional domain • A previous study determined that this was an epitope recognized by a long-term survivor				
RT(181–189)	RT(181–189 LAI)	YQYMDDLYV	HIV-1 infection	human(A*0201)	[Samri (2000)]
	• This epitope contains the mutation M184V, a frequent mutation induced by nucleoside reverse transcriptase inhibitors • High levels of recognition by ELISPOT were observed for zidovudine induced mutation YQYVDDLYV and for the wildtype peptide YQYMDDLYV in patient 250#0 (HLA-A*0201), but neither were recognized by patient 201#5 (also HLA-A*0201) • Both the wild-type and the mutated peptide were computer predicted to have a high binding affinity for A2 (http//bimas.dcrt.nih.gov/molbio/hla_bind)				
RT(192–201)	RT(192–201)	DLEIGQHRTK	HIV-1 infection	human(A3)	[Haas (1998)]
	• Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively) • New clusters of epitopes were defined utilizing different HLA molecules				
RT(192–216)	RT(359–383 HXB2)	DLEIGQHRTKIEELRQ-HLLRWGLTT	HIV-1 infection	human(Bw60)	[Menendez-Arias (1998), Walker (1989)]
	• One of five epitopes defined for RT-specific CTL clones in this study				
RT(192–216)	RT(191–215)	DLEIGQHRTKIEELRQ-HLLRWGFTT	HIV-1 infection	human(polyclonal)	[Haas (1997), Menendez-Arias (1998)]
	• Polyclonal CTL recognition switched from RT 191-215 to RT 514-524 when AZT therapy selected for the resistance mutation, and presumably the escape variant, RT T215Y				

RT(198–212)	RT( )	HRTKIEELRQHLLRW	HIV-1 infection	human( )	[Altfeld (2000)]

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined

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RT(201–209)	RT(201–209)	KIEELRQHL	HIV-1 infection	human(A2)	[Haas (1998)]

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules

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RT(201–210)	Pol( )	KIEELRQHLL		human(B58)	[De Groot (2001)]

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay
- KIEELRQHLL was newly identified as a HLA-B58 epitope in this study, it had been previously shown to be presented by HLA-A2 and Bw60
- KIEELRQHLL did not bind detectably to B7

RT(202–209)	RT( )	IEELRQHLL	HIV-1 infection	human(B60)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B60+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 1/1 group 2, and 0/0 group 3

RT(202–210)	RT(202–210 LAI)	IEELRQHLL		human(B*4001)	[Altfeld (2000), Brander & Goulder(2001)]

- C. Brander notes this is a B*4001 epitope

RT(202–210)	RT( )	IEELRQHLL	HIV-1 infection	human(B60(B*4001)	[Altfeld (2000)]

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes
- B60 is present in 10-20% of the Caucasoid and very common in Asian populations

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RT(202–210)	RT(202–210)	IEELRQHLL	HIV-1 infection	human(B60/B61)	[Day (2001)]

- No immunodominant responses were detected to five B61-restricted epitopes tested
- All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response

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RT(203–212)	RT( )	EELRQHLLRW	HIV-1 infection	human(B44)	[Menendez-Arias (1998), van der Burg (1997)]

- The only epitope recognized by CTL from a long-term survivor in two samples taken six years apart
- Recognized by CTL from a progressor, EILKEPVGHGV and TWETWWTEYW were also recognized

RT(209–220)	RT(209–220)	LLRWGLTTPDKK	HIV-1 infection	human(A2)	[Haas (1998)]

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules

RT(243–252)	RT( )	PIVLPEKDSW	HIV-1 infection	human(B*5701)	[Menendez-Arias (1998), van der Burg (1997)]

- Recognized by CTL from a progressor and a long-term survivor, KITTESIVIW was also recognized

RT(243–252)	RT( )	PIVLPEKDSW	HIV-1 infection	human(B*5701)	[Menendez-Arias (1998), van der Burg (1997)]

- Recognized by CTL from a long-term survivor whose CTL response persisted for more than 10 years – the substitution V3M reduced affinity but was well recognized; on the other hand V3T and D8G did not reduce affinity, but abrogated CTL response

RT(243–252)	RT(410–419)	PIVLPEKDSW	HIV-1 infection	human(B57)	[Oxenius (2000)]

- Epitope name: PIV. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- None of the 8 study subjects recognized this epitope but none were HLA B57+

RT(244–252)	RT(399–407)	IVLPEKDSW		human(B*5701)	[Brander & Goulder(2001)]

- Subtype of B57 not determined
- C. Brander notes this is a B*5701 epitope

RT(244–252)	RT(244–252 LAI)	IVLPEKDSW	HIV-1 infection	human(B*5701, B*5801)	[Klein (1998)]

- This peptide was defined as the optimal epitope
- B57 has been associated with long-term non-progression in the Amsterdam cohort.
- The most pronounced CTL responses in HLA B*5701 LTS were to RT and Gag
- B57 restricted CTL responses are targeted at multiple proteins, but one LTS had a response that was dominated by reactivity to the epitope – two variants were found in this LTS: ITLPEKESW, which bound to B*5701 with similar affinity as the index peptide but was an escape mutant that was not recognized by CTL, and IMLPEKDSW, which bound to B*5701 with reduced affinity but could still be recognized

- In an additional HIV+ LTS, only the variant IELPEKDSW was found, and this epitope was recognized by CTL but had less affinity for B*5701 than the index peptide
- This epitope was recognized in the context of both HLA-B*5701 and B*5801

RT(244–252)	Pol(244–252)	IVLPEKDSW	HIV-1 infection	human(B*5801)	[Appay (2000)]

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV
- HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

RT(244–252)	RT(399–407)	IVLPEKDSW		human(B57)	[van der Burg (1997)]
RT(245–252)	Pol( )	IVPEKDSW	HIV-1 infection	human(B57)	[Kostense (2001)]

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional
- In 15 of the patients, the proportion of IFNγ producing tetramer cells correlated with AIDS-free survival

RT(260–271)	RT(415–426 IIIB)	LVGKLNWASQIY	HIV-1 infection	human(B*1501)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*1501 epitope

RT(260–271)	RT(260–271)	LVGKLNWASQIY	HIV-1 infection	human(B62)	[Day (2001)]

- No immunodominant responses were detected to four B62-restricted epitopes tested

RT(260–271)	RT(415–426 IIIB)	LVGKLNWASQIY	HIV-1 infection	human(Bw62)	[Brander & Walker(1996), Menendez-Arias (1998)]

- P. Johnson, Pers. Comm.

RT(263–271)	RT(263–271 LAI)	KLNWASQIY		human(A*3002)	[Brander & Goulder(2001), Goulder (2001b)]

- C. Brander notes this is an A*3002 epitope

RT(263–271)	RT( )	KLNWASQIY	HIV-1 infection	human(A*3002)	[Goulder (2001a)]

- Epitope name: KY9 (RT-35). HLA-A*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule
- A rapid method was developed combining ELISPOT with intracellular IFN-γ staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood

- Two individuals were studied: Subject 199 (HLA A*0201/*3002 B*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A*3002/ B53/*5801 Cw4/7) an African-Caribbean
- In both HLA-A*3002 individuals the response to RSLYNTVATLY was dominant
- In subject 199 four additional A*3002 epitopes were identified
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)

RT(268–282)	RT( )	SQIYPGIKVRQLCKL	HIV-1 infection	human( )	[Altfeld (2001a)]

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses is underestimated if accessory proteins are not included in the study
- RT peptides SQIYPGIKVRQLCKL and WKGSPAIFQSSMTKI were recognized

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RT(269–277)	( )	QIYPGIKVR		(A3)	[Altfeld(2000), Brander & Goulder(2001)]

RT(269–277)	RT(269–277)	QIYPGIKVR	HIV-1 infection	human(A3)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant

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RT(271–279)	( )	YPGIKVRQL	HIV-1 infection	human(B*4201)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*4201 epitope

RT(271–279)	RT(438–446 IIIB)	YPGIKVRQL	HIV-1 infection	human(B42)	[Menendez-Arias (1998), Wilson (1996)]

- YAGIKVRQL and YPGIKVKQL are naturally occurring variants that are both reactive
- YHKIKVRQL is a naturally occurring variant that has not been tested
- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study

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RT(271–279)	Pol(438–446 IIIB)	YPGIKVRQL	HIV-1 infection	human(B42)	[Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- An additional variant that gave a positive CTL response: YPGIKVKQL, YAGIKVRQL
- YHGIKVRQL was an escape mutant

RT(293–301)	Pol(448–456 SF2-24)	IPLTEEAEL	HIV-1 infection	human(B*3501, B*5101)	[Tomiyama (2000b)]

- Epitope name: HIV-B35-SF2-24. This epitope is naturally processed and presented by both HLA-B*3501 and HLA-B*5101 and is cross-recognized by a single CTL clone
- IPLTEEAEL binds approximately four times more effectively HLA-B*3501 than HLA-B*5101

RT(293–301)	RT(448–456 SF2)	IPLTEEAEL	HIV-1 infection	human(B*3501)	[Menendez-Arias (1998), Tomiyama (1997)]

- A CTL clone responsive to this epitope was obtained
- Only 1/7 B35-positive individuals had a CTL response to this epitope
- An E to K substitution at position 5 abrogates specific lysis, but not binding to B*3501
- An I to V substitution at position 1, P to Q at position 2, and E to K at 5, abrogates specific lysis and binding to B*3501
- An I to V substitution at position 1 did not alter reactivity
- Reviewed in [Menendez-Arias (1998)], this epitope lies in the thumb region of RT

RT(293–301)	( )	IPLTEEAEL	HIV-1 infection	human(B35)	[Kawana (1999)]

- HLA B35 is associated with rapid disease progression
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals but this was one of the six that had no B35 associated pattern of mutation

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RT(293–301)	RT(448–456 SF2)	IPLTEEAEL	HIV-1 infection	human(B35, B51)	[Menendez-Arias (1998), Shiga (1996)]

- Binds HLA-B*3501 and B*5101
- Reviewed in [Menendez-Arias (1998)], this epitope lies in the thumb region of RT

RT(293–301)	Pol(447–455)	IPLTEEAEL	HIV-1 exposed seronegative, HIV-1 infection	human(B51)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

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RT(294–318)	RT(461–485 HXB2)	PLTEEAELELAENREIL-KEPVHGVY	HIV-1 infection	human(A2)	[Menendez-Arias (1998), Walker (1989)]

- One of five epitopes defined for RT-specific CTL clones in this study

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RT(308–317)	RT( )	EILKEPVGHV	HIV-1 infection	human(A*0201)	[Menendez-Arias (1998), van der Burg (1997)]

- Recognized by CTL from a long-term survivor, SPIETVPVKL was also recognized
- Recognized by CTL from a progressor, EELRQHLLRW and TWETWWTEYW were also recognized

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RT(309–317) RT(476–484) ILKEPVHGV HIV-1 infection human(A*02) [Huang (2000)]

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed
- Increases in γ interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-γ-production ELISPOT

RT(309–317) RT(476–484) ILKEPVHGV HIV-1 infection human(A*02) [Rinaldo (2000)]

- Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that persist after therapy and long periods of virus being below the level of detection

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RT(309–317) RT( ) ILKEPVHGV HIV-1 infection human(A*02) [Scott-Algara (2001)]

- Epitope name: IV9. This study examined CTL responses in HLA A*02+ children by tetramer staining for HLA-A2 immunodominant epitopes SLYNTVATL and ILKEPVHGV
- 71% of the 28 HIV-1 infected HLA-A*02 positive children recognized both epitopes, with cells from 26 children stained positive by the gag tetramer (SLYNTVATL) and 21 children by the pol tetramer (ILKEPVHGV)
- There were no differences observed in children that had therapy versus those that did not
- Tetramer-binding cells were memory activated CD28-, CD45RO+, CD45RA- HLADR+, CD69-, CD8+ T-cells

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RT(309–317) ( ) ILKEPVHGV HIV-1 infection human(A*0201) [Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

RT(309–317) Pol(476–484) ILKEPVHGV HIV-1 infection human(A*0201) [Spiegel (2000)]

- High levels of CD8+ HIV-1 specific and cytomegalovirus specific CTL were detected by HLA-A*0201-peptide tetramers in 3 infected subjects with very low CD4 counts, but CD8 T-cell mediated effector activity was not seen
- Thus HIV-1 specific CD8+ cells may be present but may lack direct effector activity in late disease, suggesting that overcoming antigen unresponsiveness may be a useful therapeutic strategy

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RT(309–317) Pol(476–484) ILKEPVHGV HIV-1 infection human(A*0201) [Sewell (1999)]

- Proteasome regulation influences epitope processing and could influence immunodominance
- The proteasome is inhibited by lactacystin treatment, and γ IFN induces expression of proteasome subunits, LMP2 and LMP7, which combine with the proteasome to create an immunoproteasome
- IFN-γ induction of the immunoproteasome and lactacystin inhibition increases the presentation of the A*0201 VIYQYMDDL epitope, but decreases the presentation of the A*0201 ILKEPVHGV epitope, which is immunodominant within pol proteins, showing the two epitopes are processed by different pathways
- ILKEPVHGV seems to be processed by the classical proteasome pathway, while VIYQYMDDL appears to be destroyed by this pathway
- This epitope contains the catalytic site (YMDD) of RT, a conserved sequence in HIV-1 which restricts escape mutants

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RT(309–317) Pol(476–484) ILKEPVHGV HIV-1 infection human(A*0201) [Loing (2000)]

- The ILKEPVHGV was modified by the addition of an N-palmitoyl-lysine residue at the P0, P1 or P10 positions of the parent peptide to create a lipopeptide for direct antigen delivery to the cytoplasm for processing
- The N-terminal modification increased the life span for functional CTL recognition up to 48 hours in comparison to the parent peptide

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RT(309–317) Pol(510–518) ILKEPVHGV Vaccine human(A*0201) [Larsson (1999)]

Vaccine: *Vector/type:* vaccinia, canarypox *HIV component:* Gag, Pol, Nef, Env

- ELISPOT was used to assay the CD8 T-cell response to the HIV-1 proteins Gag, Pol, Nef or Env expressed in vaccinia or canarypox vectors in 19 HIV+ people
- The highest CTL frequency was directed at Pol epitopes
- In A*0201 individuals, higher numbers of spot-forming T-cells were directed against HIV-1 proteins expressed in vaccinia than to peptides SLYNTVATL and ILKEPVHGV presented by A2

RT(309–317) RT(476–484) ILKEPVHGV HIV-1 infection human(A*0201) [Wilson (1998a)]

- HIV+ individuals were followed longitudinally using MHC tetramers in combination with 14 anti-BV chain MAbs, and clonal expansion of HIV-specific T-cells was followed *in vivo*
- Seven HIV+ people were studied, and all showed expansions of particular TCR BV clones, often several, relative to uninfected controls
- Three patients were followed in detail, TCR VB expansions persisted for 2 to 3 years, with occasional transient increases

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RT(309–317) RT(476–484) ILKEPVHGV HIV-1 infection human(A*0201) [Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- 2/11 of the A2+ individuals responded to ILKEPVHGV, and neither of these two responded to SLYNTVATL

RT(309–317) Pol( ) ILKEPVHGV HIV-1 infection human(A*0201) [Gray (1999)]

- Administration of highly active antiretroviral therapy (HAART) reduced CD8+ cell frequency, and the CD8+ cells detected by tetramer staining were likely to be memory cells, indicating that persistently replicating viral populations are needed to maintain high frequencies of HIV-1 specific CTL

RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Menendez-Arias (1998), Ogg (1998b)]

- HLA-tetrameric complexes were used in a cross-sectional study of 14 untreated HLA A*0201 positive individuals, revealing an inverse relationship between HIV Gag and Pol specific CTL effector cells (CTLe) and viral load
- Inclusion of both the p17 SLYNTVATL and RT ILKEPVHGV epitopes gives a good representation of HLA A*0201-restricted activity
- No correlation was observed between the CTLe and CD4 count or clearance rate of productively infected cells

RT(309–317)	RT( )	ILKEPVHGV	Vaccine	human(A*0201)	[Hanke (1998a), Hanke (1998b)]

Vaccine: *Vector/type:* vaccinia *HIV component:* polyepitope

- This epitope was shown to be processed and presented to appropriate CTL clones upon infection of human target cells with vaccinia virus Ankara (VVA) carrying 20 HIV-1 epitopes recognized by humans

RT(309–317)	RT(476–484)	ILKEPVHGV	*in vitro* stimulation	human(A*0201)	[Konya (1997), Menendez-Arias (1998)]

- This epitope was included as a positive control
- Binding affinity to A*0201 was measured, $C\_1/2\text{max}\mu M = 12$

RT(309–317)	RT(468–476)	ILKEPVHGV	*in vitro* stimulation	human(A*0201)	[van der Burg (1996)]

- Immunogenic in humans, slow dissociation rate, and associated with immunogenicity in transgenic HLA-A*0201/K^b mice
- CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual

RT(309–317)	RT(468–476)	ILKEPVHGV	*in vitro* stimulation	human(A*0201)	[van der Burg (1995)]

- Binds HLA-A*0201 – CTL generated by *in vitro* stimulation of PBMC from an HIV negative donor

RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Menendez-Arias (1998), Pogue (1995)]

- Mutational study: position 1 I to Y increases complex stability with HLA-A*0201

RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Goulder (1997e), Goulder (1997a), Menendez-Arias (1998)]

- Identical twin hemophiliac brothers were both infected with the same batch of factor VIII
- One had a response to gag A2 epitope SLYNTVATL, the other to pol A2 epitope ILKEPVHGV
- Viral sequencing from the twin that had no response to SLYNTVATL indicated his virus had the substituted form SLHNAVAVL
- 71% of an additional set of 22 HIV-1 infected HLA-A*0201 positive donors preferentially responded to gag SLYNTVATL
- Those individuals with a pol ILKEPVHGV response tended to have mutations in or around SLYNTVATL
- [Goulder (1997a)] is a review of immune escape that summarizes this study

RT(309–317)	RT(309–317)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Altman (1996)]

- This paper introduces the tetramer methodology which permits quantification of specific CTL based on expression of specific TCRs – HLA-A2 tetramers were prepared that can stain CTL lines specific for ILKEPVHGV and SLYNTVATL, and quantify HIV-specific CD8+ cell lines in freshly isolated PBMCs
- Three patients only stained the Gag epitope SLYNTVATL, one patient had the highest frequency of tetramer staining to the Pol epitope (0.77%), less to the Gag epitope (0.28%)
- The A2-Pol CD8+ clones were CD45RO positive and HLA-DR and CD38 negative, suggesting a memory rather than effector phenotype

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RT(309–317)	RT(476–484)	ILKEPVHGV	*in vitro* stimulation	human(A*0201)	[Menendez-Arias (1998), Walter (1997)]

- HLA-A2 heavy chain and β2-microglobulin expressed in *E. coli* were refolded in the presence of this peptide
- The HLA-A2-peptide complex elicited HLA-A2 peptide-specific CTL response in cells lacking HLA-A2
- Suggests that preformed HLA-peptide complexes could provide an alternate to intracellular processing for immunogens

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RT(309–317)	RT(464–472)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Gray (1999)]

- Peptide-tetramer complexes of A*0201 and SLYNTVATL or ILKEPVHGV were used to study individuals receiving HAART to determine the frequency of Class I HLA-restricted anti-HIV CD8+ T-cells
- 17/18 asymptomatic patients had a CTL response to one or both epitopes – 72% had a CTL response to SLYNTVATL
- After HAART, the majority of the epitope-specific CTL were apparently memory cells

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RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Brander (1998), Brander & Goulder(2001)]

- Of 17 infected HLA A*0201 subjects, 13 had CTL responses against the p17 SLYNTVATL epitope, six recognized ILKEPVHGV and five recognized VIYQYMDDL, and there was no correlation between viral load and recognition of a specific epitope or evidence of immune escape
- Only one subject had CTL against all three epitopes
- Subjects were part of the San Francisco City Clinic Cohort, the ARIEL project and from the Boston area
- C. Brander notes this is an A*0201 epitope

RT(309–317)	Pol(476–484)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Ogg (1999)]

- CTL effector levels were measured after potent ARV therapy using HLA-tetramer complexes for the A*0201 epitopes SYLVANTVATL and ILKEPVHGV in seven patients, and the B*3501 epitope DPNPQEVVL in one additional patient
- Levels of CTL effectors typically decline for 5-7 days and then rebound, fluctuating during the first two weeks of therapy
- After the early fluctuation, there was a steady exponential decay with a median half-life of 45 days

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RT(309–317)	RT(476–484 LAI)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*0201 epitope

RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection, *in vitro* stimulation	human(A*0201)	[Dela Cruz (2000)]

- Epitope name: IV9. Integration of HIV RT CTL epitopes into the N-terminus of the HLA-A2 heavy chain, or tethering the epitopes to the target chain, resulted in epitope-specific lysis by CD8+ CTL
- These antigens could also be used to stimulate primary responses *in vitro*

RT(309–317)	RT(309–317)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Samri (2000)]

- Epitope name: P1. The epitope was recognized by patient 250#0 but not in another A*0201+ patient, 201#5, in a study of the effects of therapy escape mutations on CTL recognition

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RT(309–317)	Pol( )	ILKEPVHGV	*in vitro* stimulation	human(A*0201)	[Engelmayer (2001)]

- Recombinant canarypox virus vector containing HIV-1 sequences, upon infection of mature dendritic cells, can trigger specific lysis through *in vitro* by T-cells from HIV-1 infected individuals at levels comparable to the response seen to HIV carried in vaccinia vectors
- Recombinant canarypox virus vector containing HIV-1 sequences can also stimulate HIV-specific CD4+ helper T-cell responses

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RT(309–317)	Pol( )	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Gea-Banacloche (2000)]

- In a study including many long-term non-progressors, no correlation between plasma virus levels and number of HIV-specific CD8+ T-cells was found
- High frequencies of circulating CD8+ T-cells were HIV-1 specific, and the majority of these responses were to gag-pol gene products
- 4/21 subjects were HLA-(A*0201), and of these only 2 subjects (patients 3 and 19) tested positive to this epitope

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RT(309–317)	Pol(476–484)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Jin (2000a)]

- The CTL effector levels (CTLe) were compared in long term non-progressors (LTNP) with low viral load and in patients whose virus was well-suppressed by therapy, using a tetramer assay
- LTNPs have high memory CTLe numbers and low viral load, while HAART patients had low CTLe numbers and low viral load

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RT(309–317)	Pol(476–484)	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Appay (2000)]

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV
- HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

RT(309–317)	Pol( )	ILKEPVHGV	HIV-1 infection	human(A*0201)	[Ostrowski (2000)]

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T-cell help in 9/10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T-cell help to a variable degree in most of patients
- Those CTL that didn't respond to CD40LT could expand with IL-2 present, and IL-15 produced by dendritic cells also contributes
- The T-helper epitope used for CD4+ T-cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKANSKFIGITE)

RT(309–317)	RT(476–484 LAI)	ILKEPVHGV	HIV-1 infection	human(A*0201, A*0205)	[Mollet (2000)]

- Epitope name: P1. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using tetramer staining or CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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RT(309–317)	Pol(476–484)	ILKEPVHGV	Vaccine	human(A2)	[Woodberry (1999)]

Vaccine: *Vector/type:* vaccinia *HIV component:* polyepitope

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested
- ILKEPVHGV was recognized by 2 of the patients

RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A2)	[Kolowos (1999)]

- TCR usage in CTL specific for this epitope was examined in three patients and identical Vβ6.1 and Vα2.5 gene segments were used and two of the patients had very similar complementarity-determining regions – clonal expansion of RT-HIV-specific CTL can contribute to the skewed TCR repertoire in HIV-1 infected patients
- CTL clones from all three patients showed similar sensitivity to mutation in the epitope, `-------E-` was well recognized (the sequence from SF2), `---D-----` was not (the common A clade form)

RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A2)	[Collins (1998)]

- Nef down-regulates MHC class I molecules, which inhibits CTL killing of HIV-infected targets
- The anti-RT CTL clone killed Nef- cells less efficiently than anti-gag clones, correlated with the reduced expression of RT

RT(309–317)	RT(476–484 LAI)	ILKEPVHGV	HIV-1 infection	human(A2)	[Fan (1997)]

- The capacity of dendritic cells to process and present antigen and stimulate anti-HIV-1 CTL memory responses was studied

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RT(309–317)	RT(464–472)	ILKEPVHGV	HIV-1 infection	human(A2)	[Kundu (1998b)]

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated
- ILKEPVHGV is a conserved HLA-A2 epitope included in this study – 5/6 patients had this sequence as their HIV direct sequence, and these had a detectable CTL response– one person carried the form ILREPVHGV and had no detectable CTL

RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A2)	[Menendez-Arias (1998), Tsomides (1994)]

- CTL clones recognize naturally processed peptide – peptide abundance corresponded to level of CTL killing

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RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 exposed seronegative	human(A2)	[Rowland-Jones (1998a)]

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating
- The A subtype consensus is ILKDPVHGV
- The D subtype consensus is identical to the epitope ILKEPVHGV

RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A2)	[Cao (1997), Menendez-Arias (1998)]

- The consensus peptides of B and D clade viruses and some As have the sequence ILKEPVHGV
- The consensus peptide of a subset of A clade viruses, ILKDPVHGV, is not cross-reactive

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RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A2)	[Menendez-Arias (1998), Yang (1996)]

- CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones
- The distinction was thought to be due to lower expression of RT relative to Env and Gag
- CTL can lyse infected cells early after infection, possibly prior to viral production

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RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A2)	[Yang (1997a)]

- CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*
- CTL produced HIV-1-suppressive soluble factors – MIP-1α, MIP-1β, RANTES, after antigen-specific activation
- CTL suppress HIV replication more efficiently in HLA-matched cells

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RT(309–317)	RT(309–317)	ILKEPVHGV	HIV-1 infection	human(A2)	[Menendez-Arias (1998), Moss (1995)]

- Two clones were obtained with different TCR usage, V_β1 and V_β21

RT(309–317)	RT(476–484)	ILKEPVHGV	HIV-1 infection	human(A2)	[Menendez-Arias (1998), Musey (1997)]
• Cervical CTL clones from an HIV-infected woman recognized this epitope					
RT(309–317)	RT(476–484 LAI)	ILKEPVHGV	HIV-1 infection	human(A2)	[Menendez-Arias (1998), Tsomides (1991)]
• Precise identification of the nonamer that binds to A2					
RT(309–317)	RT(476–484 LAI)	ILKEPVHGV	Peptide-HLA interaction	human(A2)	[Connan (1994), Menendez-Arias (1998)]
• Promotes assembly of HLA-A2 molecules in T2 cell lysates					
RT(309–317)	RT(510–518)	ILKEPVHGV	*in vitro* stimulation	human(A2)	[Parker (1992)]
• Studied in the context of HLA-A2 peptide binding					
RT(309–317)	Pol(476–484)	ILKEPVHGV	HIV-1 infection	human(A2)	[Dyer (1999)]
• CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective • Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load					
RT(309–317)	RT(476–484)	ILKEPVHGV	*in vitro* stimulation	human(A2)	[Zarling (1999)]
• This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses • Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA • A weak response to KLTPLCVSL was stimulated using macrophages as the APC • No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL					
RT(309–317)	RT( )	ILKEPVHGV	computer prediction	(A2)	[Schafer (1998)]
• This study uses EpiMatrix for T-cell epitope prediction to identify possible HLA-B27 and A-2 CTL epitopes in HIV • Based on EpiMatrix predictions, 28 peptides were synthesized and tested using T2 binding assays for potential HLA A2 or B27 binding, and 12 of these were shown to bind to the predicted HLA molecule • Two of these 12 peptides had been previously identified as CTL epitopes: HLA-B27 KRWILGLNK and HLA-A2 ILKEPVHGV • This sequence is not conserved between clades, but is found only in a small number of B clade isolates					
RT(309–317)	RT( )	ILKEPVHGV	HIV-1 infection	human(A2)	[Altfeld (2001d)]
• Epitope name: RT IV9. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested					

- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- This peptide binds to four HLA-A2 supertype alleles: A*0201, A*0202, A*0206 (highest affinity) and A*6802
- RT IV9 was recognized in 7/22 patients with chronic HIV-1 infection
- 1/13 patients with acute HIV-1 infection recognized RT IV9

RT(309–317) Pol( ) ILKDPVHGV HIV-1 infection human(A2) [Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- ILKDPVHGV or ILKEPVHGV was recognized in 1 of the 6 women (ML1760), and the response was present in the last available sample prior to seroconversion, 12 months
- 20/20 sequences of the infecting strain had no substitutions in this epitope, all were ILKDPVHGV, so there was no evidence for escape
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized by 4/22 HEPS control sex workers: ML887, ML1192, ML1250, and ML1749

RT(309–317) RT(476–484) ILKEPVHGV HIV-1 infection human(A2) [Oxenius (2000)]

- Epitope name: ILK. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- One of the 2/8 HLA-A2+ study subjects recognized this CTL epitope
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDLWIYHTQGYFPDWQNY, and GEIYKRWII and all responses declined during therapy initiated at day 390 but were restored when therapy became intermittent

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RT(309–317) Pol( ) ILKEPVHGV HIV-1 infection human(A2) [Kostense (2001)]

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional
- In 15 of the patients, the proportion of IFNγ producing tetramer cells correlated with AIDS-free survival

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RT(309–317) Pol( ) ILKEPVHGV HIV-1 infection human(A2) [Seth (2001)]

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized

- 6/10 A*0201+ individuals had HIV-specific tetramer staining cells, and 5 of these 6 declined upon successful therapy
- 3/10 A*0201+ individuals with chronic HIV-1 infection recognized this epitope
- Prior to therapy, the mean percentage of CD8+ cells that recognized the immunodominant epitope SLYNVATL was six-fold greater than the percentage recognizing the epitope ILKEPVHGV

RT(309–317) RT(476–484 SF2) ILKEPVHGV HIV-1 infection human(A2) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 0/6 group 2, and 3/4 group 3

RT(309–317) Pol(476–484) ILKDPVHGV HIV-1 exposed seronegative, HIV-1 infection human(A2) [Kaul (2001a)]

- Variants ILK(D/E)PVHGV are A/B clade specific
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-A2 women, 7/10 HEPS and 14/26 HIV-1-infected women recognized this epitope, and ILK(D/E)PVHGV tended to be more reactive in HEPS women, SL(F/Y)NTVATL in infected women
- The dominant response to this HLA allele was to this epitope in all 7/10 HEPS cases but in only 5 of the 14/26 HIV-1-infected women
- Four epitopes were considered to be “resistant epitopes”, as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILKD/EPVHGV in RT, A*6802 DTVLEDINL in Protease, B14 DLNM/TLNI/VV in p24 and B18 FRDYVDRFY/FK also in p24
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort
- Subject ML 1250 had an A2 response to ILKD/EPVHGV prior to seroconversion, which switched to SLF/YNTVATL post-seroconversion
- Subject ML 1760 had an A2 response to ILKD/EPVHGV prior to seroconversion, and gained responses to epitopes A2 SLF/YNTVATL and B27 KRWIIL/MGLNK post-seroconversion

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RT(309–317)	Pol( )	ILRIPVHGV	HIV-1 infection	human(A2)	[Sriwanthana (2001)]

- Epitope name: P464-472. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2

RT(309–317)	Pol( )	ILRIPVHGV	HIV-1 infection	human(A2)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested
- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by two amino acids: ILKEPVHGV
- This epitope was not conserved in many subtypes, and exact matches were very rare

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RT(309–317)	RT(309–317)	ILKEPVHGV	HIV-1 infection	human(A2)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person

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RT(309–317)	Pol(476–484)	ILKEPVHGV	HIV-1 infection	human(A2 supertype)	[Propato (2001)]

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)

RT(309–317)	Pol(464–472)	ILKEPVHGV	HIV-1 infection	human(A2, A*0201)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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RT(309–317)	Pol( )	ILKEPVHGV	HIV-1 exposed seronegative	human(A2, A*0202)	[Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among B and D clade viruses

- Clade A version of the epitope, ILKDPVHGV, was preferentially recognized by CTL

RT(309–317)	RT(309–317)	ILKEPVHGV	Vaccine, *in vitro* stimulation	human, murine(A2, A2 transgenic)	[De Berardinis (2000)]

Vaccine: *Vector/type:* HIV-1 peptide in filamentous bacteriophage major coat protein *HIV component:* RT peptides

- Epitope name: RT2. Phage display of the CTL epitope, ILKEPVHGV coupled with T helper epitope KDSWTVNDIQKLVGK, elicited specific CTL responses *in vitro* in PBMC from HIV negative individuals and *in vivo* upon immunization of HLA-A2 transgenic mice
- Bacteriophage presentation of peptides is generally used for stimulation of antibodies, and this novel discovery of CTL epitope processing and presentation suggests new possibilities for these vectors

RT(309–317)	Pol( )	ILKEPVHGV	Vaccine	SJL/J HLA transgenic mice(A2.1)	[Ishioka (1999)]

Vaccine: *Vector/type:* DNA *HIV component:* polyepitope

- A minigene vaccine construct encoding 6 HLA 2.1 and 3 HLA A11 restricted CTL epitopes, the universal Th cell epitope PADRE (pan-DR epitope) and an ER translocating signal sequence was constructed
- The epitopes were chosen for dominant recognition by CTLs during HBV and HIV infections in humans
- HLA transgenic mice were used for quantitating *in vivo* immunogenicity of DNA vaccines encoding HLA-restricted CTL epitopes – strong responses were observed to all nine epitopes, and CTL memory persisted up to four months after a single injection

RT(309–318)	RT(476–485 LAI)	ILKEPVHGVY	HIV-1 infection	human(B*1501)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*1501 epitope

RT(309–318)	RT(309–318)	IKLEPVHGVY	HIV-1 infection	human(B62)	[Day (2001)]

- No immunodominant responses were detected to four B62-restricted epitopes tested

RT(309–318)	RT(476–485 LAI)	ILKEPVHGVY	HIV-1 infection	human(Bw62)	[McMichael & Walker(1994), Menendez-Arias (1998)]

- Review of HIV CTL epitopes

RT(328–336)	RT(175–183 SF2)	NPDIVIYQY	HIV-1 infection	human(B35)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 1/1 group 3

RT(328–352)	RT(495–515 LAI)	EIQKQGQGQWTYQIY-QEPFKNLKTG	HIV-1 infection	human(A11)	[Menendez-Arias (1998), Walker (1989)]
• One of five epitopes defined for RT-specific CTL clones in this study					
RT(340–350)	RT(507–516)	QIYQEPFKNLK	HIV-1 infection	human( )	[Menendez-Arias (1998), Price (1995)]
• Study of cytokines released by HIV-1 specific activated CTL					
RT(340–350)	Pol(487–497 93TH253 CRF01)	QIYQEPFKNLK	HIV-1 exposed seronegative, HIV-1 infection	human(A11)	[Sriwanthana (2001)]
• Epitope name: P495-505. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand • HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed • This epitope was weakly reactive in the HEPS study subject 128 who was HLA A11/A33 • This epitope was reactive in HIV+ study subjects 053 and 184 who carried HLA-A11					
RT(340–350)	Pol(487–497 93TH253 CRF01)	QIYQEPFKNLK	HIV-1 infection	human(A11)	[Bond (2001)]
• HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive • Seventy-seven possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified • This epitope was not predicted by the EpiMatrix method to be likely to bind to A11, though it served as an epitope in the FSWs, and it was one of the six A11 epitopes that had been previously defined • 5/8 tested FSWs recognized this epitope • This epitope was highly conserved in other subtypes, although exact matches were not very common					
RT(340–352)	RT(507–519 LAI)	QIYQEPFKNLKTG	HIV-1 infection	human(A11)	[Johnson & Walker(1994), Menendez-Arias (1998)]
• This epitope was listed in a review					
RT(340–352)	Pol(495–507)	QIYQEPFKNLKTG	HIV-1 infection	human(A11)	[Ferrari (2000)]
• One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles					
RT(341–350)	RT(508–516)	IYQEPFKNLK	HIV-1 infection	human(A*1101)	[Culmann(1998)]
• C. Brander notes that this is an A*1101 epitope in the 1999 database					

RT(341–350)	RT(508–517 LAI)	IYQEPFKNLK	HIV-1 infection	human(A*1101)	[Brander & Goulder(2001)]
• C. Brander notes this is an A*1101 epitope					
RT(341–350)	RT(508–517 SF2)	IYQEPFKNLK	HIV-1 infection	human(A11)	[Altfeld (2001c)]
• Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection • The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef • Previously described and newly-defined optimal epitopes were tested for CTL response • Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 1/2 group 3					
RT(341–350)	Pol(508–516)	IYQEPFKNLK	HIV-1 exposed seronegative, HIV-1 infection	human(A11)	[Kaul (2001a)]
• ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers					
RT(356–365)	Pol(511–520 HXB2)	RMRGAHTNDV	HIV-1 infection	human(A*3002)	[Mulligan (2001)]
• Epitope P52 from Patient 11113 with HLA genotypes A*2904, A*3002, B*1503, B*5802, Cw*0202, Cw*0602					
RT(364–372)	RT(518–526 U455)	DVKQLTEVV		human(A28, A*6802)	[Dong(1998), Menendez-Arias (1998)]
• Predicted on binding motif, no truncations analyzed • Reacts with clade A consensus (U455), and with the peptide DVKQLAEAV, from the D clade					
RT(364–372)	RT(470–478 clade A)	DVKQLTEVV	HIV-1 infection	human(B70)	[Dorrell (1999)]
• CTL responses in three individuals with non-clade B infections were studied, two with subtype A infections, one with subtype C – their infections all originated in East Africa • This CTL response was defined in a patient with an A subtype infection • Bulk cultures from this patient gave a CTL response that could recognize the subtype D form of this epitope, with two substitutions (DVKQLAEAV), though a CTL line from these cultures didn't recognize the B clade variant (DVKQLTEAV)					
RT(374–383)	RT( )	KITTESIVIW	HIV-1 infection	human(B*5701)	[Menendez-Arias (1998), van der Burg (1997)]
• Patients studied were from the Amsterdam cohort • CTL epitopes of 3 rapid progressors were compared to 4 long-term survivors (LTS); no differences could be found in the degree of conservation in the two groups • Epitope recognized by LTS and by a progressor					

RT(374–383)	RT( )	KITTESIVIW	HIV-1 infection	human(B*5701)	[van der Burg (1997)]

- Recognized by CTL from a progressor and a long-term survivor, PIVLPEKDSW was also recognized

RT(375–383)	RT(375–383 LAI)	ITTESIVIW	HIV-1 infection	human(B*5701 B*5801)	[Klein (1998)]

- Another patient recognized the ten-mer version of this epitope, KITTESIVIW [van der Burg (1997)]
- B57 has been associated with long-term non-progression in the Amsterdam cohort
- The most pronounced CTL responses in HLA B*5701 LTS were to RT and Gag
- The patient that recognized ITTESIVIW also recognized IVLPEKDSW

RT(375–383)	RT(375–383 SF2)	ITTESIVIW	HIV-1 infection	human(B57)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/2 group 3

RT(392–401)	RT(559–568 LAI)	PIQKETWETW		human(A*3201)	[Harrer (1996b), Menendez-Arias (1998)]

- Reviewed in [Menendez-Arias (1998)], suggest the epitope is HLA B53/Cw2
- C. Brander notes that this is an A*3201 epitope in the 1999 database

RT(392–401)	RT(559–568 LAI)	PIQKETWETW		human(A*3201)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*3201 epitope

RT(392–401)	Pol(547–556 HXB2)	PIQKETWETW	HIV-1 infection	human(A*3201)	[Mulligan (2001)]

- Epitope P55 from Patient 07118 with HLA genotypes A*0209, A*3201, B*4002, B*5301, Cw*0202, Cw*0401
- Epitope P55 Patient 07118 has 4 more optimal peptides N10, KEKGGLEGL with HLA B*4002; G21 and G22, AEWDRVHPV with HLA B*4002; G31, QASQEVKNW with HLA B*5301;G43, TERQANFL with HLA B*4002

RT(392–401)	RT(559–568 SF2)	PIQKETWETW	HIV-1 infection	human(A32)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response

- Number of HLA-A32+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 1/1 group 2, and 0/0 group 3

RT(397–406)	RT( )	TWETWWTEYW	HIV-1 infection	human(B44)	[Menendez-Arias (1998), van der Burg (1997)]

- Recognized by CTL from two progressors
- EILKEPVGHGV and EELRQHLLRW were also recognized by one, and RETKLGKAGY was also recognized by the other

RT(416–424)	Pol(563–571 93TH253 CRF01)	FVNTPPLVK	HIV-1 exposed seronegative	human(A11)	[Sriwanthana (2001)]

- Epitope name: P571-579. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was weakly reactive in the HEPS study subject 128 who was HLA A11/A33

RT(416–424)	Pol(563–571 93TH253 CRF01)	FVNTPPLVK	HIV-1 infection	human(A11)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 1/8 tested FSWs recognized it
- This epitope was conserved many subtypes (but not subtype H), but exact matches were not very common

RT(421–429)	RT(421–429)	PLVKLWYQL	HIV-1 infection	human(A2)	[Haas (1998)]

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules

RT(432–440)	RT(587–597 SF2)	EPIVGAETF	HIV-1 infection	human(B*3501)	[Menendez-Arias (1998), Tomiyama (1997)]

- A CTL clone responsive to this epitope was obtained
- 5/7 B35-positive individuals had a CTL response to this epitope
- An E to D substitution at position 1, and V to I at position 4, reduces activity but not binding to B*3501
- [Menendez-Arias (1998)] note in their review that this epitope is near the protease cleavage site and conservation of this region is important for proper viral maturation

RT(432–440)	Pol(587–595)	EPIVGAETF	HIV-1 infection	human(B*3501)	[Tomiyama (2000a)]

- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A

- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

RT(432–440) ( ) EPIVGAETF HIV-1 infection human(B35) [Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

RT(432–440) Pol(587–595) EPIVGAETF HIV-1 infection human(B35) [Dyer (1999)]

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load

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RT(432–440) RT(587–596 SF2) EPIVGAETF HIV-1 infection human(B35, B51) [Shiga (1996)]

- Binds HLA-B*3501, and is also presented by B51 – but CTL could not kill RT-vaccinia virus infected cells that expressed B51

RT(432–440) Pol(587–595) EPIVGAETF HIV-1 infection human(B35, B51) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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RT(432–441) Pol(587–596) EPIVGAETFY HIV-1 infection human(B*3501) [Tomiyama (2000a)]

- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

RT(432–441)	RT(587–597 SF2)	EPIVGAETFY	HIV-1 infection	C3H/HeJ mice(B35)	[Menendez-Arias (1998), Shiga (1996)]

- Binds HLA-B*3501, but not presented by B51, in contrast to the peptide EPIVGAETF
- [Menendez-Arias (1998)] note in their review that this epitope is located near the protease cleavage site and conservation of this region is important for viral maturation
- This epitope spans the Pol p66 RT – p15 (RNAse) domain

RT(432–441)	RT(587–597 SF2)	EPIVGAETFY	HIV-1 infection	human(B35)	[Kawana (1999)]

- HLA B35 is associated with rapid disease progression
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation

RT(434–447)	RT( )	IVGAETFYVDGAAS	HIV-1 infection	human(A*6802)	[Menendez-Arias (1998), van der Burg (1997)]

- Recognized by CTL from a long-term survivor that recognized a set of 5 overlapping peptides spanning IVGAETFYVDGAAS as well as PIVLPEKDSW and KITTESIVIW
- A*6802 is a subset of HLA-A28
- This epitope spans the Pol p66 RT – p15 (RNAse) domain

RT(436–445)	RT(591–600 IIIB)	GAETFYVDGA	HIV-1 infection	human(B45)	[Menendez-Arias (1998)]

- This epitope spans the Pol p66 RT – p15 (RNAse) domain

RT(436–445)	Pol(591–600 IIIB)	GVETFYVDGA	HIV-1 infection	human(B45)	[Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- No variants of this epitope were found in a non-transmitting mother who had a CTL response to it
- This epitope spans the Pol p66 RT – p15 (RNAse) domain

RT(437–445)	Pol(592–600 HXB2)	AETFYVDGA	HIV-1 infection	human(B*4501)	[Mulligan (2001)]

- Epitope P59 from Patient 07107 with HLA genotypes A*3002, A*3201, B*4501, B*5301, Cw*0401, Cw*1202

RT(437–447)	RT(592–602 LAI)	AETFYVDGAAN		human(A28)	[Brander & Walker(1996), Menendez-Arias (1998)]

- P. Johnson, pers. comm.
- This epitope spans the Pol p66 RT – p15 (RNAse) domain

RT(437–447)	Pol(592–602)	AETFYVDGAAN	HIV-1 infection	human(A28)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

RT(438–448)	RT(593–603 IIIB)	ETFYVDGAANR	HIV-1 infection	human(A26)	[Menendez-Arias (1998)]
	• This epitope spans the Pol p66 RT – p15 (RNAse) domain				
RT(438–448)	Pol(593–603 IIIB)	ETFYVDGAANR	HIV-1 infection	human(A26)	[Wilson (1999a)]
	• This study describes maternal CTL responses in the context of mother-to-infant transmission • Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants • One other variant was found that gave a positive, though reduced, CTL response: ETYYVNGAANR • This epitope spans the Pol p66 RT – p15 (RNAse) domain				
RT(448–457)	RT( )	RETKLGKAGY	HIV-1 infection	human(A29)	[van der Burg (1997)]
	• Patients studied were from the Amsterdam cohort • CTL epitopes of 3 rapid progressors were compared to 4 long-term survivors (LTS) and no differences could be found in the degree of conservation in the two groups • Epitope recognized by an LTS • This epitope occurs in the p15 (RNAse) domain of Pol p66 RT				
RT(449–457)	Pol(604–612 HXB2)	ETKLGKAGY	HIV-1 infection	human(A*2601)	[Mulligan (2001)]
	• Epitope P61 from Patient 02112 with HLA genotypes A*3303, A*2601, B*5801, B*8201, Cw*0302, Cw*07(01, 06) • Epitope P61 Patient 02112 has an other optimal peptide N11, DILDLWIF with HLA Cw*0701 and Cw*0706				
RT(481–505)	RT(648–672)	AIYLALQDSGLEVNIV-TDSQYALGI	HIV-1 infection	human( )	[Menendez-Arias (1998), Price (1995)]
	• Study of cytokines released by HIV-1 specific activated CTL • This epitope occurs in the p15 (RNAse) domain of Pol p66 RT				
RT(481–505)	RT(648–672 PV22)	AIYLALQDSGLEVNIV-TDSQYALGI	HIV-1 infection	human(B14)	[Kalams (1994), Menendez-Arias (1998)]
	• A CTL response used to study gene usage in HLA-B14 response • This epitope occurs in the p15 (RNAse) domain of Pol p66 RT				
RT(485–493)	RT(640–648 HXB2R)	ALQDSGLEV	Vaccine	human(A2)	[Brander (1995)]
	Vaccine: *Strain:* HXB2 *HIV component:* RT • Epitope studied in the context of inclusion in a synthetic vaccine • This epitope occurs in the p15 (RNAse) domain of Pol p66 RT				
RT(485–493)	RT(640–648 HXB2R)	ALQDSGLEV	HIV-1 infection	human(A2.1)	[Brander (1995), Brander (1996)]
	• This epitope was recognized by PBMC from 3/14 HIV+ asymptomatic patients				

- This epitope was used along with Env CTL epitope TLTSCNTSV and a tetanus toxin T helper epitope for a synthetic vaccine
- This vaccine failed to induce a CTL response, although a helper response was evident
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT

RT(485–505) RT(648–672) ALQDSGLEVVTDSQY-ALGI HIV-1 infection human(B14) [Brander & Walker(1995)]

- Unpublished, S. Kalams
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT

RT(496–504) Pol(651–659 HXB2) VTDSQYALG HIV-1 infection human(B*1503) [Mulligan (2001)]

- Epitope P66 from Patient 03115 with HLA genotypes A*3002, A*68(011, 08), B*0801, B*1503, Cw*07(01, 06), Cw*08(02, 05)

RT(496–505) Pol( ) VTDSQYALGI HIV-1 exposed seronegative human(B14, B*1402) [Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among A, B and D clade viruses

RT(496–505) RT(663–672 IIIB) VTDSQYALGI HIV-1 infection human(Cw8) [Brander & Walker(1996)]

- Unpublished, P. Johnson
- Published in this database in 1995 as B14, but B14 transfected cells did not present the peptide and it is thought to be presented by the genetically linked Cw8 molecule instead [Brander & Walker(1996)]
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT

RT(496–505) RT( ) VTDSQYALGI HIV-1 exposed seronegative human(Cw8) [Rowland-Jones (1998a)]

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating
- The A and D subtype consensus are identical to the B clade epitope
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT

RT(509–518) Pol( ) QPDKSESELV human(B7) [De Groot (2001)]

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay
- QPDKSESELV was newly identified as an HLA-B7 epitope in this study

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RT(516–525)	RT(516–525)	ELVNQIIEQL	HIV-1 infection	human(A2)	[Haas (1998)]
	• Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively) • New clusters of epitopes were defined utilizing different HLA molecules • This epitope occurs in the p15 (RNAse) domain of Pol p66 RT				
RT(520–528)	Pol(520–528 LAI)	QIIEQLIKK		human(A*1101)	[Brander & Goulder(2001), Fukada (1999)]
	• C. Brander notes this is an A*1101 epitope				
RT(530–538)	Pol(685–693 HXB2)	KVYLAWVPA	HIV-1 infection	human(A*0301)	[Mulligan (2001)]
	• Epitope P69 from Patient 07124 with HLA genotypes A*0202, A*0301, B*4501, B*5301, Cw*1502, Cw*0401				
RT(532–540)	Pol(714–722)	YLAWVPAHK	HIV-1 infection	human(A3 supertype)	[Propato (2001)]
	• Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes • Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs • A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus • This epitope can bind 5/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)				
RT(532–540)	RT(532–540)	YLAWVPAHK	HIV-1 infection	human(B7)	[Haas (1998)]
	• Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively) • New clusters of epitopes were defined utilizing different HLA molecules • This epitope occurs in the p15 (RNAse) domain of Pol p66 RT				

Table 11: **Integrase**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Integrase(20–28)	Pol(762–770)	RAMASDFNL	HIV-1 infection	human(A2 supertype)	[Propato (2001)]
• Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes • Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs • A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus • This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)					
Integrase(22–31)	Pol(764–773)	MASDFNLPPV	HIV-1 infection	human(A2 supertype)	[Propato (2001)]
• Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes • Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs • A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus • This epitope can bind five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)					
Integrase(28–36)	Pol(743–751 SF2)	LPPVVAKEI	HIV-1 infection	human(B*5101)	[Tomiyama (1999)]
• HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995) • 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3% • Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed • Four of the six epitopes were highly conserved among B subtype sequences – LPPVVAKEI is highly conserved					
Integrase(82–89)	RT(797–804 SF2)	GYIEAEVI	HIV-1 infection	human(A*2402)	[Ikeda-Moore (1997)]
• Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402 • This peptide induced CTL in 1/4 HIV-1+ people tested • GYIEAEVI bound to A*2402 weakly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained					
Integrase(89–98)	Pol( )	IPAETGQETA		human(B56)	[De Groot (2001)]
• The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes • A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay					

	• IPAETGQETA was newly identified as an HLA-B56 epitope in this study				
Integrase(96–104)	Integrase(823–831)	ETAYFILKL		human(A*6802)	[Dong & Rowland-Jones(1998)]
	• Epitope found in clade A, B, and D – Pers. Comm. S. Rowland-Jones and T. Dong				
Integrase(96–104)	Pol( )	ETAYFILKL	HIV-1 exposed seronegative	human(A*6802)	[Kaul (2000)]
	• 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses • Low risk individuals did not have such CD8+ cells • CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women				
Integrase(96–104)	Pol( )	ETAYFILKL	HIV-1 infection	human(A*6802)	[Kaul (2001b)]
	• This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative • The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire • This epitope was recognized in 1/22 HEPS sex worker controls (ML1671)				
Integrase(96–104)	Pol(744–752)	ETAYFILKL	HIV-1 infection	human(A*6802)	[Appay (2000)]
	• This epitope is newly-defined in this study • Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV • HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation • In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α				
Integrase(96–105)	Pol(744–752)	ETAYFYILKL	HIV-1 exposed seronegative, HIV-1 infection	human(A*6802)	[Kaul (2001a)]
	• ETAYFYILKL cross-reacts with clades A, B and D • ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers				

- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-A*6802 women, 3/12 HEPS and 9/11 HIV-1-infected women recognized this epitope likelihood ratio 7.9, p value 0.01, and HEPS women tended to respond to DTVLEDINL, while infected women to ETAYFYILKL
- The dominant response to this HLA allele was to this epitope in 2 of the 3/12 HEPS cases and in all 9/11 HIV-1-infected women that responded to the epitope
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV
- Subject ML 1707 started with a CTL response to A*6802 DTVLEDINL prior to seroconversion, and switched to A*6802 ETAYFILKL and A24 RDYVDRFFKTL post-seroconversion
- Subject ML 1830 made no detectable response prior to seroconversion, but responded to A*6802 DTVLEDINL and A*6802 ETAY-FILKL post-seroconversion

Integrase(127–135)	Pol(869–877)	KAACWWAGI	HIV-1 infection	human(A2 supertype)	[Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)

Integrase(173–181)	Pol(888–896)	KTAVQMAVF	human(B*5701)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*5701 epitope
- Epitope is motif based, personal communication from C. Hay

Integrase(173–181)	Pol(888–896)	KTAVQMAVF	human(B57)	[Hay(1999)]

- Epitope is motif based, personal communication from C. Hay

Integrase(177–186)	Pol(919–928)	QMAVFIHNFK	HIV-1 infection	human(A3 supertype)	[Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 5/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

Integrase(178–186)	Pol(920–928)	MAVFIHNFK	HIV-1 infection	human(A3 supertype)	[Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

Integrase(179–187)	Pol(921–929)	AVFIHNFKR	HIV-1 infection	human(A3 supertype)	[Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 5/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

Integrase(179–188)	Integrase(179–188 LAI)	AVFIHNFKRK		human(A*1101)	[Brander & Goulder(2001), Fukada (1999)]

- C. Brander notes this is an A*1101 epitope

Integrase(179–188)	Pol(894–903 93TH253 CRF01)	AVFIHNFKRK	HIV-1 exposed seronegative	human(A11)	[Bond (2001)]

- Epitope name: P894-903. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was weakly reactive in the HEPS study subjects 265 who was HLA A2/A11 and 128 who was HLA A11/A33, and had been predicted to be a possible A11 epitope using Epimer in [Bond (2001)]

Integrase(219–227)	Pol(934–942 HXB2)	KIQNFRVYY	HIV-1 infection	human(A*3002)	[Mulligan (2001)]
	• Epitope P94 from Patient 11102 with HLA genotypes A*0205, A*3002, B*1402, B*5301, Cw*0802, Cw*0401				
Integrase(219–228)	Pol(919–928)	KIQNFRVYYR	HIV-1 infection	human(A3 supertype)	[Propato (2001)]
	• Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes • Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs • A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus • This epitope can bind 5/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)				
Integrase(241–249)	Pol(576–584)	LLWKGEGAV	*in vitro* stimulation	human(A*0201)	[van der Burg (1996)]
	• Slow dissociation rate, associated with immunogenicity in transgenic HLA-A*0201/K^b mice • CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual				
Integrase(241–249)	Pol(956–964)	LLWKGEGAV	HIV-1 infection	human(A2)	[Kundu (1998b)]
	• Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients • 1/6 showed increased Env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated • LLWKGEGAV is a conserved HLA-A2 epitope included in this study – 6/6 patients had this sequence as their HIV direct sequence, but only four of these had a detectable CTL response				
Integrase(241–249)	Pol(956–964 HXB2R)	LLWKGEGAV	Peptide-HLA interaction	human(A2)	[Parker (1992), Parker (1994)]
	• Studied in the context of HLA-A2 peptide binding				
Integrase(241–249)	Pol(956–964 HXB2R)	LLWKGEGAV	Peptide-HLA interaction	human(A2)	[Brander (1995)]
	• No CTL activity found in HIV-infected subjects, epitope studied in the context of inclusion in a synthetic vaccine				
Integrase(241–249)	Pol(956–964)	LLWKGEGAW	HIV-1 infection	human(A2, A*0201)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				

Table 12: **Pol**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Pol( )	RT( )		HIV-1 infection	human( )	[Buseyne (1998a)]
• This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load					
Pol( )	p66( )		HIV-1 infection	human( )	[Zheng (1999)]
• Protein delivery (gp160 LAV, p66 LAV, and p24 NY5) to human dendritic cells (DC) with liposomes provides enhanced memory CTL response relative to delivery of protein alone • Chloroquine administration enhanced epitope presentation, and brefeldin A and peptide aldehyde inhibitors inhibited antigen presentation, suggesting epitopes were processed by a classical proteasome pathway					
Pol( )	Pol( )		HIV-1 infection	human( )	[Wasik (2000)]
• HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of β-chemokines and IL-2 relative to other HIV+ infants • No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors • CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccinia/HIV constructs					
Pol( )	Pol( )		Vaccine	human( )	[Salmon-Ceron (1999)]
Vaccine: *Vector/type:* canarypox *Strain:* LAI, MN *HIV component:* gp41, Gag, Pro, V3 • The vaccine used was a rec canarypox with HIV-1 gp120 MN, tm/gag/protease LAI (vCP205), alone or with p24E-V3 MN synthetic peptide (CLTB-36)) • Twenty HIV negative subjects were vaccinated in phase I trial with combinations of vCP205 and CLTB-36 • Immunization with vCP205 induced HIV-1-specific ABs to gp160, V3, and p24 antigens, and CTL immune responses against vCP205 were detected after the fourth immunization in 33% of the subjects against Env, Gag and Pol, but the CLTB-36 peptide did not produce AB or CTL immune responses against p24 or gp160					
Pol( )	Pol(172–219 clade B)		Vaccine	human( )	[Gorse (1999)]
Vaccine: *Vector/type:* canarypox prime with rgp120 boost *Strain:* LAI and SF2 *HIV component:* Env, Gag, Pro, Nef, Pro • The vaccine used was rec canarypox expressing HIV-1 env, gag, pol, nef and protease (vCP300) with or without administration of HIV-1 SF-2 rgp120 • In vitro inducible CTL activity against HIV-1 Env, Gag, Pol, and Nef antigens was observed in 79% (15/19) of vaccine recipients • The combination of vCP300 and vP1291 together resulted in an overall increase in CTL induction and detection sensitivity					

Pol( ) Pol( ) HIV-1 infection human( ) [Betts (1999)]
- This study demonstrated an inverse correlation between HIV Type I plasma viral load and CTL activity directed against HIV-1 Pol, and stronger combined effects of Pol- and Env-specific CTL, in long-term survivors (LTS) of HIV-1 infection

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Pol( ) Pol( ) HIV-1 infection human( ) [Aladdin (1999)]
- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death

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Pol( ) RT( ) HIV-1 infection human( ) [Buseyne (1998b)]
- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes

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Pol( ) RT( ) Vaccine murine( ) [Kim (1997b)]

Vaccine: *Vector/type:* DNA *HIV component:* Gag, Pol, Vif, Env *Stimulatory Agents:* B7, IL-12
- A gag/pol, vif or gp160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice
- When IL-12 was present, CTL response could be detected even without *in vitro* stimulation

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Pol( ) RT( ) HIV-1 infection human( ) [Trickett (1998)]
- Twelve HIV-1 infected patients were re-infused with their own lymphocytes, cryopreserved from an earlier time point in the infection
- Improvement in CD4+ and CD8+ T-cells were seen in 7/12, and an increase in the CTL response to Pol was seen in one patient

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Pol( ) RT( ) HIV-1 infection human( ) [Froebel (1997)]
- Two HIV-1 infected children with contrasting disease courses were followed longitudinally – one died of AIDS, the other is a long-term non-progressor
- Reactivity against Gag, Pol, Env and Tat proteins was tested by PBMC bulk cultured cells reacting with protein expressed in vaccinia constructs in autologous EBV transformed B cells
- The child who progressed consistently had CTL against Pol and Tat
- The long-term non-progressing child had no detectable CTL, but was heterozygous for a mutation in the CCR5 receptor and for HLA-B49, which has been shown to be associated with slower progression

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Pol( ) Pol( ) HIV-1 infection human( ) [Betts (1997)]
- 6/8 individuals from Zambia infected with C clade virus had CTL that were able to make response to B clade HIV-1 IIIB vaccinia-expressed Gag, Pol and Env proteins
- A vigorous cross-clade response was not limited to a particular protein, and the level of recognition of different proteins varied among the six patients

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Pol( ) RT( ) HIV-1 infection human( ) [De Maria (1997)]
- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T-cell function

- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels

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Pol( ) Pol( ) HIV-1 exposed seronegative human( ) [Goh (1999)]

- 13/37 exposed uninfected individuals with repeated high-risk sexual exposure had HIV-1 specific CTL against Env, Gag, Pol, or a combination of proteins – CTL activity was correlated with a CCR5 wildtype genotype
- In this group, the highest CTLp frequencies were directed at Gag, but the most common response was to Env and four individuals had responses to multiple HIV-1 proteins

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Pol( ) Pol( ) Vaccine human( ) [Evans (1999)]

Vaccine: *Vector/type:* canarypox *HIV component:* gp120, gp41, Gag, Pro, Nef, RT

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination

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Pol( ) Gag/Pol( ) Vaccine chimpanzee( ) [Kim (1998)]

Vaccine: *Vector/type:* DNA *HIV component:* Env, Gag, Pol *Stimulatory Agents:* CD86, CD80

- The study explores the use of co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses

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Pol( ) Pol( ) HIV-1 infection human( ) [Jin (1998a)]

- CTL precursor frequencies were determined in HIV-1 infected pregnant women, and significantly higher CTLp frequencies to Pol and Nef were found in non-transmitting mothers than in transmitting mothers;

Pol( ) Pol( ) none HIV-1 infection human( ) [Young (2001)]

- Addition of recombinant human IL-12 (rhIL-12) to cultures increased HIV-specific lysis of HIV-Gag, Pol and gp120 vaccinia expressed antigens (11/15 tested increased lysis by > 5%) if the culture was derived from HIV+ individuals who had CD4 cells/μl > 500
- 2/10 individuals with <200 CD4 cells/μl, and 3/10 individuals with 200-500 CD4 cells/μl, had an increase of >5% upon treatment of the culture with rhIL-12, so a few individuals in late stage disease had CD8 cells that maintained responsiveness to rhIL-12

Pol( ) RT( ) HIV-1 infection human( ) [Cao (2000)]

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent-specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype

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Pol( ) Pol( ) HIV-1 infection human( ) [White (2001)]

- HIV-specific CTL activity was detected in the female reproductive tract of only 1/3 HIV-infected women who underwent a hysterectomy, although CTL could be identified in the PBMC of all three women

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Pol( )	Pol( )	HIV-1 infection	human( )	[Jin (2000a)]

- The CTL precursor level (CTLp) was measured in long term non-progressors (LTNP) with low viral load using limiting dilution analysis and measuring CTL against Env Gag and Pol expressed in vaccinia in autologous targets
- LTNPs have high memory CTL numbers and low viral load

Pol( )	Pol( )	HIV-1 exposed seronegative	human( )	[Rowland-Jones (2001)]

- This is a review that summarizes observations about HIV-specific CTL found in the HIV-1 exposed persistently seronegative (HEPS) population
- The CTL responses assayed by ELISPOT and by CTL precursor frequencies by limiting dilution analysis indicate that CTL in HEPS individuals tend to be of a lower magnitude than in chronic HIV-1 infections – the responses in HEPS cases are below the level of detection by tetramer assays
- CD8+ CTL responses tend to be detectable in HEPS subjects only if they are recently exposed, and the response diminishes if exposure is reduced – it is not clear if there is a stable memory population in HEPS cases
- CD8+ CTL responses in the HEPS population are associated with HIV-1 specific CD4+ T-cell responses, assayed by proliferation assays, IL-2 secretion, and ELISPOT, and the authors consider the possibility that HIV-1-specific T-help responses improve the "quality" of the CD8+ response in HEPS individuals relative to HIV-1 infected individuals, who tend to have a poor HIV-1-specific T-help response
- HIV-1 specific CD8+ CTL responses in HIV-1 infected individuals show reduced levels of perforin, and the T-cells may not mature properly, and although similar studies have not been conducted in HEPS individuals this is considered as a possible difference in the CTL immune response in HEPS and HIV-1 infected people

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Pol( )	Pol( )	HIV-1 infection	human(A*0201, Cw*08)	[Shacklett (2000)]

- HIV-1 specific, MHC class I-restricted CTL killing was detected in duodenal and rectal gut associated lymphoid tissue (GALT) sites from three infected individuals – the distribution of class I restricted CTL was different in the peripheral blood samples and GALT samples

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Pol( )	Pol( )	Vaccine	murine(H-2^d)	[Huang (2001)]

Vaccine: *Vector/type:* DNA *Strain:* gag HxB2, pol NL43 *HIV component:* Gag, Pol

- Mice were immunized with four humanized DNA constructs: GagPol, that would form a pseudoparticle carrying Gag and Pol, Gag, Pol or a GagPol fusion construct
- The GagPol pseudoparticle, Gag and GagPol fusion construct all elicited strong anti-Gag CTL, but only the GagPol fusion construct elicited strong anti-Pol CTL

Table 13: **Vif**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Vif(17–26)	Vif(17–26 SF2)	RIRTWKSLVK	HIV-1 infection	human(A*0301)	[Altfeld (2001a)]
	• Epitope name: RK10. CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals • 10/29 (35%) individuals tested responded to Vif • This epitope was recognized by 3/15 individuals expressing A*0301 allele • HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses is underestimated if accessory proteins are not included in the study • Overlapping Vif peptides QVDRMRIRTWKSLVK and RIRTWKSLVKHHMYI both reacted with T-cells from AC-06 and contained epitope RIRTWKSLVK				
Vif(17–26)	( )	RIRTWKSLVK		(A3)	[Altfeld(2000), Brander & Goulder(2001)]
Vif(31–39)	Vif(31–39 SF2)	ISKKAKGWF	HIV-1 infection	human(B*5701)	[Altfeld (2001a)]
	• CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals • 10/29 (35%) individuals tested responded to Vif • This epitope was recognized by 2/6 individuals carrying the B*5701 allele				
Vif(48–57)	Vif(48–57 SF2)	HPRVSSEVHI	HIV-1 infection	human(B*0702)	[Altfeld (2001a)]
	• Epitope name: HI10. CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals • 10/29 (35%) individuals tested responded to Vif • This epitope was recognized by 3/8 individuals carrying the B*0702 allele • HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses is underestimated if accessory proteins are not included in the study • Overlapping Vif peptides HHYESTHPRVSSEVH and THPRVSSEVHIPLG both reacted with T-cells from AC-06 and contained epitope HPRVSSEVHI				
Vif(102–111)	Vif(102–111 SF2)	LADQLIHLHY	HIV-1 infection	human(B*1801)	[Altfeld (2001a)]
	• CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals • 10/29 (35%) individuals tested responded to Vif • This epitope was recognized by 2/5 individuals carrying the B*1801 allele				
Vif(160–169)	Vif( )	KPPLPSVKKL		human(B7)	[De Groot (2001)]
	• The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes				

- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay
- KPPLPSVKKL was newly identified as an HLA-B7 epitope in this study

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Vif( ) Vif( ) Vaccine murine( ) [Kim (1997b)]

Vaccine: *Vector/type:* DNA *HIV component:* Gag, Pol, Vif, Env *Stimulatory Agents:* B7, IL-12

- A gag/pol, vif or env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice
- When IL-12 was present, CTL response could be detected even without *in vitro* stimulation

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Vif( ) Vif( ) Vaccine murine(H-2^d) [Ayyavoo (2000)]

Vaccine: *Vector/type:* DNA *HIV component:* Vif, Vpu, Nef

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-γ levels
- Antigen stimulation increased IFN-γ production in pVVN-P immunized mice, indicating a Th1 response
- IL-4 production was not significantly changed after antigen stimulation compared to control levels
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization-stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell

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Table 14: **Vpr**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Vpr(12–20)	Vpr(12–20 SF2)	REPHNEWTL	HIV-1 infection	human(B*4002)	[Altfeld (2001a)]
	• CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals • Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection • Only one B*4002+ individual was tested, and had a CTL response against REPHNEWTL • Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells				
Vpr(30–38)	Vpr(29–38 SF2)	AVRHFPRIW	HIV-1 infection	human(B*5701)	[Altfeld (2001a)]
	• CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals • This epitope was recognized by 4/6 individuals carrying the B*5701 allele • Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection • Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells				
Vpr(34–42)	Vpr(34–42 SF2)	FPRIWLHGL	HIV-1 infection	human(B*0702, B*8101)	[Altfeld (2001a)]
	• Epitope name: FL9. CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals • This epitope was recognized by 2/2 individuals carrying the B*8101 allele and 4/8 individuals carrying the B*0702 allele • Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection • Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells • HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses is underestimated if accessory proteins are not included in the study • FPRIWLHGL was the only epitope identified in Vpr for AC-06				
Vpr(59–67)	Vpr(58–66 LAI)	AIIRILQQL		human(A*0201)	[Altfeld (2001b), Brander & Goulder(2001)]
	• C. Brander notes this is an A*0201 epitope				
Vpr(59–67)	Vpr(58–66 SF2)	AIIRILQQL	HIV-1 infection	human(A*0201)	[Altfeld (2001a)]
	• Epitope name: AL9. CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals • This epitope was recognized by 8/24 individuals expressing A*0201 allele				

- Epitope is located within a highly conserved α-helix in Vpr
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells
- The A2 epitopes Vpr AIIRLLQQL and p17 SLYNTVATL do not account for the dominance of Vpr and p17, the result holds even when HLA-A2+ individuals are excluded

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Vpr(59–67) Vpr( ) AIIRILQQL HIV-1 infection human(A*0201) [Altfeld (2001d)]

- Epitope name: Vpr-59. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- AIIRILQQL binds to four HLA-A2 supertype alleles: A*0203, A*0201, A*0206 and A*6802 (highest affinity), but not A*0202
- 5/22 individuals with chronic HIV-1 infection recognized this epitope, but with low magnitude responses in ELISPOT
- 2/12 HLA-A2 patients with acute HIV-1 infection responded strongly to this peptide, but during chronic infection SL9 and Gag-386 tended to be immunodominant while Vpr-59 was weak and sub-dominant
- One of the the acutely infected individuals, AC13, was HLA A*0201/68 B44/14 and also had a strong acute response to gp41 epitope SV10 SLLNATDIAV
- This peptide was shown to be properly processed and presented in TAP-competent B-cell lines *in vitro*

Vpr(59–67) Vpr( ) AIIRILQQL HIV-1 infection human(A2) [Goulder (2001b)]

- Epitope name: AL9. Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation

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Vpr(59–67) Vpr(59–67 SF2) AIIRILQQL HIV-1 infection human(A2) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 0/6 group 2, and 0/4 group 3

Vpr(59–67) Vpr(59–67) AIIRILQQL HIV-1 infection human(A2 supertype) [Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes

- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind four of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)

Vpr(62–70) Vpr( ) RILQQLLFI HIV-1 infection human(A*0201) [Altfeld (2001d)]

- Epitope name: Vpr-62. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- This epitope binds to three HLA-A2 supertype alleles: A*0202, A*6802 (strongest affinity) and A*0203
- 3/22 chronically infected patients had a weak ELISPOT response to this epitope
- 0/12 HLA-A2 patients with acute HIV-1 infection responded to this peptide

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Vpr(62–70) Vpr(62–70) RILQQLLFI HIV-1 infection human(A2 supertype) [Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)

Table 15: **Tat**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Tat(2–11)	( )	EPVDPRLEPW		(B53)	[Addo (2001), Brander & Goulder(2001)]
Tat(2–11)	Tat(2–11 BRU)	EPVDPRLEPW	HIV-1 infection	human(B53)	[Addo (2001)]
• Epitope name: Tat 1. Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides • 11/57 (19.3%) HIV-1+ individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide • EPVDPRLEPW ws recognized by four individuals, but only two were B53, thus this epitope can probably be presented by other HLA alleles					
Tat(36–50)	( )	VCFQTKGLGISYGRK		human( )	[Novitsky (2001)]
• This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort • 17 of 46 patient reacted with Tat immunodominant peptide VCFQTKGLGISYGRK • Most of the CTL responses occurred despite a mismatch between the autologous viral sequence and peptide – complete matches were seen only in 4/19 cases (21%) and the mismatched CTL tended not to respond to the autologous viral peptide indicative of immune escape					
Tat(38–47)	( )	FQTKGLGISY		human(B*1503)	[Novitsky (2001)]
• Epitope name: T38-FY10. This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort • 17 of 46 patient reacted with Tat immunodominant peptide VCFQTKGLGISYGRK • FQTKGLGISY was the optimal epitope in the peptide VCFQTKGLGISYGRK among B*1503+ individuals					
Tat(49–57)	Tat(49–57)	NOT AN EPITOPE		murine( )	[Kim (1997a)]
• The Tat peptide RKKRRQRRR when conjugated to a protein can cause that protein to be taken up by APCs and presented to CTL • The system was demonstrated by vaccinating mice with an OVA-Tat peptide conjugate and immunizing H-2 K^b mice • The CTL response to the H-2 K^b specific OVA peptide SIINFEKL was stimulated					
Tat(49–57)	Tat(49–57)	RKKRRQRRR	Vaccine	murine(H-2^d)	[Billaut-Mulot (2001)]
Vaccine: *Vector/type:* DNA with DNA boost, DNA with recombinant protein boost *Strain:* LAI *HIV component:* Gag, Tat, Nef *Stimulatory Agents:* IL-18 • DNA vaccinated BALB/c mice primed and boosted with the multiepitopic vaccine with IL-18 showed lymphoproliferative responses 7 weeks post immunization • Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime/DNA boost was more effective than DNA prime protein boost • Immunization with either the multiepitopic DNA or with the mixed DNA vaccine induced HIV-1 specific Th1 cytokines (IL-2 and IFN-γ)					

- Co-administration of IL-18 increased T-cell responses but decreased anti-HIV antibody levels

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Tat(83–92) Tat( ) GPKESKKKVE human(B58) [De Groot (2001)]

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay
- GPKESKKKVE was newly identified as an HLA-B58 epitope in this study

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Tat( ) Tat( ) Vaccine human( ) [Calarota (1999)]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev Tat

- 9/9 HIV-1+ subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-γ production, and IL-6 and IgG responses
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination

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Tat( ) Tat( ) HIV-1 infection human( ) [Froebel (1997)]

- Two HIV-1 infected children with contrasting disease courses were followed longitudinally – one died of AIDS, the other is a long-term non-progressor
- Reactivity against Gag, Pol, Env and Tat proteins was tested by PBMC bulk cultured cells reacting with protein expressed in vaccinia constructs in autologous EBV transformed B cells
- The child who progressed consistently had CTL against Pol and Tat
- The long-term non-progressing child had no detectable CTL, but was heterozygous for a mutation in the CCR5 receptor and for HLA-B49, which has been shown to be associated with slower progression

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Tat( ) Tat( ) HIV-1 infection, Vaccine human( ) [Calarota & Wahren(2001)]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev, Tat *Stimulatory Agents:* CpG motifs

- This review discusses the cellular immune response, and comments on the stimulatory role of CpG motifs and how HIV-1 DNA vaccines can boost the CTL and Th proliferative responses in asymptomatic HIV+ individuals

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Tat( ) Tat( ) Vaccine macaque( ) [Cafaro (2001)]

Vaccine: *Vector/type:* DNA *Strain:* BH-10 *HIV component:* Tat *Stimulatory Agents:* CpG, ISCOM

- Macaques (*Macaca fascicularis*) were immunized with HIV-1 Tat linked to an adenovirus major late promotor in a plasmid with 23 CpG sequences, 12 unmethylated
- The vaccinated animals contained a primary infection challenge with SHIV89.6P, preventing CD4+ T-cell decline in the animals, suggesting Tat may be useful at blocking viral replication at its early stage

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Tat( )	Tat( )	Vaccine	murine(H-2^d)	[Xin (2001)]

Vaccine: *Vector/type:* adeno-associated virus (AAV) *HIV component:* Env, Tat, Rev *Stimulatory Agents:* IL-2

- An AAV vector expressing HIV-1 env, tat, and rev genes (AAV-HIV vector) was used to vaccinate BALB/c mice
- A single injection stimulated and long lasting serum IgG, fecal IgA, and HIV-specific CTL
- Boosting enhanced the humoral response, and IL-2 enhanced T-cell immunity

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Table 16: **Rev**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Rev(9–23)	Rev(9–23 HXB2)	DEELIRTVRLIKLLY	HIV-1 infection	human( )	[Blazevic (1995)]
	• Induces both Th and CTL activities, no HLA restriction analysis performed				
Rev(12–31)	Rev(11–30 SF2)	LLKAVRLIKFLYQSNP-PPNF	HIV-1 infection	human( )	[Lieberman (1997a)]
	• Of 25 patients, most had CTL specific for more than one HIV-1 protein • Only one subject (HLA-A2, A24, B13, B35) had CTL that could recognize vaccinia-expressed LAI Rev				
Rev(14–23)	Rev(14–23 clade B)	KAVRLIKFLY		human(B*5701, B*5801)	[Addo (2001), Brander & Goulder(2001)]
	• C. Brander notes this is a B*5701 and a B*5801 epitope				
Rev(14–23)	Rev(14–23 BRU)	KAVRIKLFLY	HIV-1 infection	human(B*5701, B*5801)	[Addo (2001)]
	• Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides • 11/57 (19.3%) HIV-1+ individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide • This epitope was also recognized by another individual in whom it was restricted by HLA*B5801, an allele closely related to HLA*B5701, suggesting cross-presentation by the two HLA alleles				
Rev(25–39)	Rev(25–39 HXB2)	SNPPPNPEGTRQARR	HIV-1 infection	human( )	[Blazevic (1995)]
	• Induces both Th and CTL activities, no HLA restriction analysis performed				
Rev(33–48)	Rev(33–48 HXB2)	GTRQARRNRRRRWRE-R	HIV-1 infection	human( )	[Blazevic (1995)]
	• Induces both Th and CTL activities, no HLA restriction analysis performed				
Rev(41–56)	Rev(41–56 HXB2)	RRRRWRERQRQIHSIS	HIV-1 infection	human( )	[Blazevic (1995)]
	• Induces both Th and CTL activities				
Rev(55–63)	Rev(55–63 LAI)	ISERILSTY	HIV-1 infection	human(A1)	[van Baalen (1997)]
	• Predicted to be an HLA-A1 epitope based on anchor residues 2S and 9Y • Both forms LSGWL(L or I)STY, with intact anchors, were found in an HLA-A1+ individual with Rev-responsive CTL • An HLA-A1 individual who did not make a Rev response had lost the C-term anchor, ISGWILS(T or N)S • 3/7 long-term non-progressors and 0/5 progressors were positive for HLA-B57 (associated with prolonged survival) • CTLp frequencies to Rev and Tat were inversely correlated with rapid progression to AIDS, but not Gag, RT or Nef				

Rev(55–63)	Rev(55–63)	ISERILSTY	HIV-1 exposed seronegative, HIV-1 infection	human(A1)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

Rev(67–75)	( )	SAEPVPLQL		(B14)	[Brander & Goulder(2001), van Baalen & Gruters(2000)]

Rev(67–75)	Rev( )	SAEPVPLQL	HIV-1 infection	human(B14)	[Schutten (2001)]

- Molecularly cloned primary NSI macrophage tropic strain 2.1 and SI non-macrophage tropic strain 1.2 were isolated from study participant ACH320 and use to infect irradiated XID mice that had been reconstituted with human PBMC from B14+ seronegative donors – results indicate CTL may favor selective outgrowth of macrophage tropic strains
- The CTL clone TCC108 specific for SAEPVPLQL, previously described by van Baalen 1997, and van Baalen 1998, was stimulated *in vitro* and given to the mice to apply specific CTL pressure
- The macrophage-tropic HIV-1 strain #2.1 escaped CTL pressure more efficiently (7/14 animals) than its non-macrophage-tropic counterpart #1.2 (SI) – the latter isolate was suppressed in 13/14 animals – macrophage may serve as a CTL sanctuary and reduced pressure on macrophage tropic HIV strains may allow additional replication to assist with acquisition of escape
- HIV-1 variants selectively induced by TCC108 for SI strain 1.2: SEEPVPLQL, and for strain 2.1: SAEHVPLQL, SAESVPLQL, SVEPVPLQL, SLEPVPLQL, SAEPVPFQL, and SAEPVPFQL

Rev(67–75)	Rev(67–75 IIIB)	SAEPVPLQL	HIV-1 infection	human(B14, Cw8)	[van Baalen (1998)]

- The Rev-specific CTL response studied here was from an individual infected with HIV-1 for more than 12 years without developing symptoms – Rev and Tat are expressed early and CTL activity against these proteins has been correlated with long-term survival
- The CTL clone TCC108 specific for this epitope was studied *in vitro*
- CTLs added immediately after infection suppressed viral production, indicative of CTL interference with viral production prior to lysis – CTL-mediated lysis occurred after the onset of progeny viral release, but prior to peak viral production
- Rapid selection of a E69K mutation, which abolished CTL, recognition was observed
- The epitope was originally listed as B14, but Cw8 and B14 are in linkage disequilibrium, and in this case were not distinguished (Pers. Comm., Christian Brander, 1999)

Rev(67–75)	( )	SAEPVPLQL		(Cw5)	[Addo (2001), Brander & Goulder(2001)]

Rev(67–75)	Rev( )	SAEPVPLQL	HIV-1 infection	human(Cw5)	[Goulder (2001b)]

- Epitope name: SL9. Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation

Rev(67–75)	Rev(67–75 SF2)	SAEPVPLQL	HIV-1 infection	human(Cw5)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection

- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-Cw5+ individuals that had a CTL response to this epitope broken down by group: 2/6 group 1, 0/1 group 2, and 0/2 group 3

Rev(67–75) Rev(69–77 BRU) SAEPVPLQL HIV-1 infection human(Cw8) [Addo (2001)]

- Epitope name: SL9. Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides
- 11/57 (19.3%) HIV-1+ individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide
- This epitope is the first defined HIV-specific CTL epitope resticted by HLA-Cw5
- This epitope was recognized by 2/5 individuals expressing HLA-Cw8 and by 5/11 individuals expressing Cw5 allele, which differs from Cw8 by 4 amino acids, suggesting promiscuous presentation of the epitope between those HLA molecules
- Longitudinal data was available for 6 Rev-SL9 responders, who were treated during acute infection, and the response was stable 2 and 12 months after initiaion of HAART, measurements by ELISPOT and flow-based intracellular cytokine staining (ICS) were concordant – in two subjects the response was heightened by transient reexposure to antigen with treatment interruption at 12 to 14 months

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Rev( ) Rev( ) Vaccine human( ) [Calarota (1999)]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev Tat

- 9/9 HIV-1+ subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-γ production, and IL-6 and IgG responses
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination

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Rev( ) ( ) human( ) [Novitsky (2001)]

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort
- Anti-Rev CTL responses were distributed throughout the protein and 27/47 subjects (57%) demonstrated HIV-1C Rev-specific ELISPOT CTL responses of more than 100 SFC/106 PBMC

Rev( ) Rev( ) HIV-1 infection, Vaccine human( ) [Calarota & Wahren(2001)]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev, Tat *Stimulatory Agents:* CpG motifs

- This review discusses the cellular immune response, and comments on the stimulatory role of CpG motifs and how HIV-1 DNA vaccines can boost the CTL and Th proliferative responses in asympotomatic HIV+ individuals

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Rev( )	Rev( )	Vaccine	murine(H-2^d)	[Ishii (1997)]

Vaccine: *Vector/type:* DNA with CMV promotor *HIV component:* gp160, Rev *Stimulatory Agents:* cationic liposome

- pCMV160/Rev is a DNA vaccine candidate carrying gp160 and Rev linked to a cytomegalovirus (CMV promotor)
- pCMV160/Rev given in conjunction with a cationic liposome gave enhanced DTH, Ab and CTL responses

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Rev( )	Rev( )	Vaccine	murine(H-2^d)	[Ihata (1999)]

Vaccine: *Vector/type:* DNA *HIV component:* rev *Stimulatory Agents:* CD40

- pcRev DNA i.m. vaccination in BALB/c mice induced Th1, Th2 and IgG responses, and enhanced the CTL response to Rev, but did not induce mucosal IgA

Rev( )	Rev( )	Vaccine	murine(H-2^d)	[Xin (2001)]

Vaccine: *Vector/type:* adeno-associated virus (AAV) *HIV component:* Env, Tat, Rev *Stimulatory Agents:* IL-2

- An AAV vector expressing HIV-1 env, tat, and rev genes (AAV-HIV vector) was used to vaccinate BALB/c mice
- A single injection stimulated and long lasting serum IgG, fecal IgA, and HIV-specific CTL
- Boosting enhanced the humoral response, and IL-2 enhanced T-cell immunity

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Table 17: **Vpu**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Vpu(4–13)	Vpu( )	LVILAIVALV		human(B7)	[De Groot (2001)]
	• The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes • A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay • LVILAIVALV was newly identified as an HLA-B7 epitope in this study using ELISPOT, but could not be shown to bind to B7				
Vpu( )	Vpu( )		Vaccine	murine(H-2^d)	[Ayyavoo (2000)]
	Vaccine: *Vector/type:* DNA *HIV component:* Vif, Vpu, Nef • Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-γ levels • Antigen stimulation increased IFN-γ production in pVVN-P immunized mice, indicating a Th1 response • IL-4 production was not significantly changed after antigen stimulation compared to control levels • Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization-stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell				

Table 18: **gp160**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
gp160(2–10)	gp160(2–10 IIIB)	RVKEKYQHL	HIV-1 infection	human(B*0801)	[Brander & Goulder(2001)]
	• C. Brander notes this is a B*0801 epitope				
gp160(2–10)	gp160(2–10 IIIB)	RVKEKYQHL	HIV-1 infection	human(B8)	[Sipsas (1997)]
	• HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB • Type-specific epitope, unique to the LAI and IIIB because of a deletion of three amino acids that are present in all other subtype B HIV-1s • RVKGIRKNYQHL, a variant found in JRCSF, was not recognized • This epitope is in the signal sequence of gp120				
gp160(2–10)	gp120(2–10)	RVKEKYQHL	HIV-1 infection	human(B8)	[Day (2001)]
	• B8-restricted CTL that accounted for about 1/3 of the total CTL response in one individual				
gp160(6–15)	gp120(6–15 CM243 CRF01)	TQMNWPNLWK	HIV-1 exposed seronegative	human(A11)	[Sriwanthana (2001)]
	• Epitope name: E6-15. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand • HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed • This epitope after a second stimulation *in vitro* gave a weak response in HEPS study subject 186 who was HLA A2/A11				
gp160(6–15)	gp120(6–15 CM243 CRF01)	TQMNWPNLWK	HIV-1 infection	human(A11)	[Bond (2001)]
	• HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive • 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified • This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it • This epitope was not conserved in other subtypes, and exact matches were rare				
gp160(29–49)	gp120( )	AAEQLWVTVYYGVPV-WKEAT	HIV-1 infection	human(A11)	[Weekes (1999b)]
	• Peptide 7035.1: Almost all CD8+ T-cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed in the CD28 depleted cell population • HIV CTL responses to 3 Env and 2 Gag peptides were studied				

- The clonal composition of TCR Vβ responses was studied and was found to be highly focused, with one TCR β-chain sequence tending to dominate the peptide-specific response – clones to this epitope were Vβ6

gp160(31–39)	gp120(30–38)	AENLWVTVY	HIV-1 infection	human(B44)	[Day (2001)]
gp160(31–39)	gp120(30–38 SF2)	AENLWVTVY	HIV-1 infection	human(B44)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B44+ individuals that had a CTL response to this epitope broken down by group: 1/8 group 1, 2/3 group 2, and 3/4 group 3

gp160(31–40)	gp160(30–39 WEAU)	AENLWVTVYY	HIV-1 infection	human(B*4402)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*4402 epitope

gp160(31–40)	gp160(30–39 WEAU)	AENLWVTVYY	HIV-1 infection	human(B44)	[Borrow (1997), Borrow & Shaw(1998), Goulder (1997a)]

- Two CTL lines from the patient WEAU were studied – one had an optimal peptide of (A)AENLWVTVYY, and the other (A)AENLWVTVY, and both responded equally well with one or two N-term Alanines
- Rapidly post-infection, a strong immunodominant response was observed against this epitope
- The naturally occurring forms of the peptide found in WEAU were tested as targets for early WEAU CTLs – the form TENLWVTVY was as reactive as the wild type AENLWVTVY – but the forms AKNLWVTVY, AGNLWVTVY, AANLWVTVY did not serve as targets
- The glutamic acid in the second position is a B44 anchor residue
- [Goulder (1997a)] and [Borrow & Shaw(1998)] are reviews of immune escape that summarizes this study in the context of CTL escape to fixation

gp160(31–55)	gp120(32–56 LAI)	TEKLWVTVYYGVPVW-KEATTTLFCA	Vaccine	human(B18)	[Johnson (1994a)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- HLA restricted CTL response to epitope in HIV-1 vaccinia-env vaccinees

gp160(31–55)	gp120(32–56 LAI)	TEKLWVTVYYGVPVW-KEATTTLFCA	Vaccine	human(B18)	[Ferris (1999), Hammond (1995)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- This peptide can be processed for HLA-B18 presentation by both TAP-1/2 independent and dependent pathways

gp160(33–42)	gp120(32–41 LAI)	KLWVTVYYGV	Vaccine	human(A2)	[Dupuis (1995)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- CTL from HLA-A2 positive subject react with this peptide

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gp160(33–42)	Env(32–41 clade B)	KLWVTVYYGV	HIV-1 infection, Vaccine	human(A2.1)	[Kundu (1998a)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- Ten HIV-1+ HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses

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gp160(34–55)	gp120(25–46 BRU)	LWVTVYYGVPVWKEA-TTTLFCA	HIV-1 infection	human(A2)	[Dadaglio (1991)]

- Defined through peptide blocking of CTL activity, and Env deletions

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gp160(36–46)	gp120(36–46 CM243 CRF01)	VTVYYGVPVWR	HIV-1 exposed seronegative	human(A11)	[Sriwanthana (2001)]

- Epitope name: E36-4. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope after a second stimulation *in vitro* gave a weak response in HEPS study subject 186 who was HLA A2/A11

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gp160(36–46)	gp120(36–46 CM243 CRF01)	VTVYYGVPVWR	HIV-1 infection	human(A11)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified
- This epitope was not predicted by the EpiMatrix method to be likely to bind to A11, though it served as an epitope in the FSWs, and it was one of the six A11 epitopes that had been previously defined
- 1/8 tested FSWs recognized this epitope
- This epitope was only conserved in CRF01 and subtypes B and C, and exact matches were uncommon

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gp160(36–46)	gp120( )	VTVYYGVPVWK	HIV-1 infection	human(A11 and A*6801)	[Threlkeld (1997)]

- Study of the fine specificity of an A3-like-HLA-super-type epitope (the A3-super-type includes A*0301, A*1101, A*3101, A*3301, and A*6801)
- The A3 super-type is characterized as a hydrophobic or hydroxyl containing anchor residue at position 2, and a positive charge in the C-term position
- While most lines were specific, a promiscuous cloned CTL line was derived from an HIV+ donor that could recognize this epitope presented by either A11 or A*6801

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gp160(37–46)	gp120(37–46 LAI)	TVYYGVPVWK	Vaccine	human(A*0301)	[Johnson (1994b)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- Multiple CTL clones obtained from two vaccinees
- C. Brander notes that this is an A*0301 epitope in the 1999 database

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gp160(37–46)	gp120(37–46 LAI)	TVYYGVPVWK	Vaccine	human(A*0301)	[Brander & Goulder(2001)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- C. Brander notes this is an A*0301 epitope

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gp160(37–46)	Env( )	TVYYGVPVWK	Vaccine	SJL/J HLA trans-genic mice(A11)	[Ishioka (1999)]

Vaccine: *Vector/type:* DNA *HIV component:* polyepitope

- A minigene vaccine construct encoding 6 HLA 2.1 and 3 HLA A11 restricted CTL epitopes, the universal Th cell epitope PADRE (pan-DR epitope) and an ER translocating signal sequence was constructed
- The epitopes were chosen for dominant recognition by CTLs during HBV and HIV infections in humans
- HLA transgenic mice were used for quantitating *in vivo* immunogenicity of DNA vaccines encoding HLA-restricted CTL epitopes – strong

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gp160(37–46)	gp120(37–46)	TVYYGVPVWK	Vaccine	human(A3)	[Carruth (1999)]

Vaccine: *Vector/type:* canarypox *Strain:* MN, LAI *HIV component:* gp120, gp41, Gag, Protease

- The vaccine used was a live recombinant canarypox (CP) virus vaccine containing multiple HIV-1 genes (HIV-1 MN gp120, HIV-1 LAI gp41, HIV-1 LAI Gag, HIV-1 LAI protease)
- CD4+ and CD8+ Gag and Env specific CTL responses were detected in only 1/5 vaccinated volunteers, and were not detectable 1 year after vaccination
- CTL responses to epitopes SLYNTVATL and TVYYGVPVWK from HIV+ control patients were used as positive controls
- The study explored why vaccinees were non-responsive – non-response was not due to inherent defects or differences in the ability of these individuals to process and present antigen

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gp160(37–46)	gp120(37–46 LAI)	TVYYGVPVWK	HIV-1 infection	human(A3)	[Goulder (1997e), Goulder (1997a)]

- Identical twin hemophiliac brothers were both infected with the same batch of factor VIII
- One had a response to this epitope, the other did not
- [Goulder (1997a)] is a review of immune escape that summarizes this study

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gp160(37–46)	gp120(36–45)	TVYYGVPVWK	HIV-1 infection	human(A3)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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gp160(37–46)	gp120(37–46)	TVYYGVPVWK	HIV-1 infection	human(A3)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant

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gp160(37–46)	Env(49–58)	TVYYGVPVWK	HIV-1 infection	human(A3 supertype)	[Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

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gp160(37–46)	gp120(38–41 LAI)	TVYYGVPVWK	Vaccine	human(A3.1)	[Johnson (1994a)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- Highly conserved epitope recognized by multiple CTL clones from vaccinee

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gp160(37–46)	gp120(37–46 LAI)	TVYYGVPVWK	Vaccine	human(A3.1)	[Ferris (1999), Hammond (1995)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- This peptide can be processed for HLA-A3.1 presentation by TAP-1/2 independent and dependent pathways

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gp160(37–46)	gp120(37–46 LAI)	TVYYGVPVWK	HIV-1 infection	human(B*0301)	[Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found

- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

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gp160(38–48) gp120(45–55) VYYGVPVWKEA HIV-1 infection human(Cw7) [Nehete (1998)]

- Three long-term non-progressors and one asymptomatic HIV+ individual were studied and found to have HLA class I C-restricted CD8+ Env-specific CTLs – Cw7 specific CTL were found against three peptides, including this one
- HLA-C antigens are expressed on lymphoid cells to a lesser extent than either HLA-A or -B
- HLA-C confers protection against lysis by natural killer cells and by non-MHC-restricted effector T-cells and Cw7 directly governs this resistance to lysis – the authors hypothesize that pathogens that inhibit antigen expression and class I expression may particularly down regulate Cw7, thus triggering non-MHC restricted killing

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gp160(42–51) gp120(42–51 PV22) VPVWKEATTT HIV-1 infection human(B*5501) [Brander & Goulder(2001)]

- C. Brander notes this is a B*5501 epitope

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gp160(42–51) gp120(42–51 PV22) VPVWKEATTT HIV-1 infection human(B55) [Brander & Walker(1995)]

- P. Johnson, unpublished

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gp160(42–51) gp120(41–55) VPVWKEATTT HIV-1 infection human(B55) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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gp160(42–52) gp120(42–52) VPVWKEATTTL HIV-1 infection human(B*3501) [Brander & Goulder(2001)]

- C. Brander notes this is a B*3501 epitope

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gp160(42–52) gp120(42–52 PV22) VPVWKEATTTL HIV-1 infection human(B35) [Cao (1997)]

- VPVWKEATTTL is the consensus sequence for clades B and D
- VPVWKDAETTL is the consensus sequence for clade A and it is cross-reactive
- VPVWKEADTTL is the consensus sequence for clade C and it is cross-reactive
- VPVWKEADTTL is the consensus sequence for clade E and even with three substitutions still retains some cross-reactivity

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gp160(42–52) gp120(41–51) VPVWKEATTTL HIV-1 infection human(B35) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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gp160(42–61)	gp120(49–68)	VPVWKEATTTLFCAS-DAKAY	*in vitro* simulation	human( )	[Lieberman (1995)]

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide

gp160(42–61)	gp120(49–68 SF2)	VPVWKEATTTLFCAS-DAKAY	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160
- Three of these 11 had CTL response to this peptide
- The responding subjects were HLA-A2, A3, B8, B62; HLA-A3, A24, B7, B38

gp160(42–61)	gp120(49–68 SF2)	VPVWKEATTTLFCAS-DAKAY	HIV-1 infection	human( )	[Lieberman (1997b)]

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients

gp160(50–59)	Env(62–71)	TTLFCASDAK	HIV-1 infection	human(A3 supertype)	[Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

gp160(51–59)	Env(63–71)	TLFCASDAK	HIV-1 infection	human(A3 supertype)	[Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

gp160(52–61)	gp120(59–68 HXB2)	LFCASDAKAY	HIV-1 infection	human(A*2402)	[Lieberman (1992)]

- CTL epitope defined by T-cell line and peptide mapping
- C. Brander notes that this is an A*2402 epitope in the 1999 database

gp160(52–61)	gp120(53–62 LAI)	LFCASDAKAY	HIV-1 infection	human(A*2402)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*2402 epitope

gp160(52–61)	gp120(53–62)	LFCASDAKAY	HIV-1 exposed seronegative, HIV-1 infection	human(A24)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

gp160(52–61)	gp120(53–62 LAI)	LFCASCAKAY	HIV-1 infection	human(B38)	[Shankar (1996)]
• Uncertain whether optimal, binds A24 as well					
gp160(52–71)	gp120(59–78)	LFCASDAKAYDTEVHI-NVWAT	*in vitro* simulation	human( )	[Lieberman (1995)]
• HIV-specific CTL lines developed by *ex vivo* stimulation with peptide					
gp160(52–71)	gp120(59–78 SF2)	LFCASDAKAYDTEVHI-NVWAT	HIV-1 infection	human( )	[Lieberman (1997a)]
• Of 25 patients, most had CTL specific for more than one HIV-1 protein • Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160 • One of these 11 had CTL response to this peptide • The responding subject was HLA-A2 and B-21					
gp160(62–80)	gp120(69–88 SF2)	DTEVHNVWATHACVP-TDPN	HIV-1 infection	human( )	[Lieberman (1997a)]
• Of 25 patients, most had CTL specific for more than one HIV-1 protein • Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160 • One of these 11 had CTL response to this peptide • The responding subject was HLA-A2 and B-21					
gp160(78–86)	Env(77–85)	DPNPQEVVL	HIV-1 infection	human(A*3501)	[Ogg (1999)]
• CTL effector levels were measured after potent ARV therapy using HLA-tetramer complexes for the A*0201 epitopes SYLVANTVATL and ILKEPVHGV in seven patients, and the B*3501 epitope DPNPQEVVL in one additional patient • Levels of CTL effectors typically decline for 5-7 days and then rebound, fluctuating during the first two weeks of therapy • After the early fluctuation, there was a steady exponential decay with a median half-life of 45 days					
gp160(78–86)	gp120(77–85)	DPNPQEVVL	HIV-1 infection	human(B*3501)	[Ogg (1998b)]
• This epitope was included to illustrate the specificity of HIV-tetrameric staining, in a cross-sectional study correlating HLA A*0201 CTL effector cells and low viral load					
gp160(78–86)	gp120(77–85 SF2)	DPNPQEVVL	HIV-1 infection	human(B*3501)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*3501 epitope					
gp160(78–86)	gp120(77–85 SF2)	DPNPQEVVL	HIV-1 infection	human(B*3501)	[Tomiyama (1997)]
• A CTL clone responsive to this epitope was obtained • 2/7 B35-positive individuals have a CTL response to this epitope					

- This epitope is highly variable
- The substitutions: 1N, 3S and 7I, 7L and 9M, 8I, 8K all abrogate specific CTL lysis, but of these only 8K reduces binding to B*3501
- The substitution 8V to 8E does not reduce specific CTL activity

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gp160(78–86) Env(77–85) DPNPQEVVL HIV-1 infection human(B35) [Dyer (1999)]

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load

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gp160(78–86) ( ) DPNPQEVVL HIV-1 infection human(B35) [Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

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gp160(78–86) ( ) DPNPQEVVL HIV-1 infection human(B35) [Kawana (1999)]

- HLA B35 is associated with rapid disease progression
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation

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gp160(78–86) gp120(77–85 SF2) DPNPQEVVL HIV-1 infection human(B35) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 0/1 group 3

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gp160(78–86)	gp120(77–85 SF2)	DPNPQEVVL	HIV-1 infection	human(B35, B51)	[Shiga (1996)]
• Binds HLA-B*3501 and B*5101 – CTL can kill gp120-vaccinia virus-infected cells carrying B35 or B51					
gp160(78–86)	gp120(77–85)	DPNPQEVVL	HIV-1 exposed seronegative, HIV-1 infection	human(B51)	[Kaul (2001a)]
• ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers					
gp160(103–111)	Env(102–110)	QMHEDIISL	HIV-1 infection	human(A*0201)	[Kmieciak (1998a)]
• Epitope name: 4.3. CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL – all have A2 anchor residues; • The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*; • Peptides 4.3 and D1 bound HLA-A*0201 molecules with high affinity; • Peptides 4.3 and D1 stimulated CTL with a relatively limited TCR Vβ repertoire;					
gp160(104–119)	gp120(111–126 IIIB)	MQEDIISLWDQSLKPC	*in vitro* stimulation	human( )	[Macatonia (1991)]
• Primary CTL response with cells from non-infected donors stimulated by the peptide					
gp160(105–117)	gp120( )	HEDIISLWDQSLK	HIV-1 infection	chimpanzee( )	[Lubeck (1997)]
• No epitope-specific CTL were detected in chimpanzees immunized with adenovirus-HIV-1 MN gp160 recombinant despite a response to peptides P18 and T1 • Helper and cytotoxic T-cells have been found to be stimulated by this peptide (T2)					
gp160(105–117)	gp120(112–124 IIIB)	HEDIISLWDQSLK	HIV-1 exposed seronegative	human( )	[Pinto (1995)]
• CTL and T helper cell reactivity in healthcare workers exposed to HIV					
gp160(105–117)	gp120(112–124 IIIB)	HEDIISLWDQSLK	HIV-1 infection	human(A2)	[Clerici (1991)]
• Epitope name: T2. Helper and cytotoxic T-cells can be stimulated by this peptide (T2)					
gp160(108–116)	Env(107–115 clade B)	IISLWDQSL	Vaccine	human(A2.1)	[Kundu (1998a)]
Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160 • Ten HIV-1+ HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period • Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity • Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual • CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses					

gp160(109–117)	Env(109–117 CM243 CRF01)	ISLWDQSLK	HIV-1 exposed seronegative	human(A11)	[Bond (2001)]

- Epitope name: E109-117. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was weakly reactive in the HEPS study subject 265 who was HLA A2/A11, and had been predicted to be a possible A11 epitope using Epimer in [Bond (2001)]

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gp160(112–130)	gp120(119–139 SF2)	WDQSLKPCVKLTPLC-VSLK	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160
- One of these 11 had CTL response to this peptide
- The responding subject was HLA-A2 and B-21

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gp160(117–126)	Env(72–81)	KPCVKLTPLC	HIV-1 infection	human(B7)	[Jin (2000b)]

- This B7 epitope is one of three subdominant CTL responses detected in a long-term non-progressor
- A dominant B7 epitope was defined using conventional methods, and three additional sub-dominant HLA B7 epitopes were defined by first using a non-anchor based strategy, EpiMatrix, to identify 2078 possible epitopes in the autologous HIV-1, followed by B7 anchor residue prediction to narrow the set to 55 peptides for experimental testing

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gp160(121–129)	Env(120–128)	KLTPLCVTL	HIV-1 infection	human(A*0201)	[Kmieciak (1998a)]

- Epitope name: D1. CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL – all have A2 anchor residues;
- The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*;
- Peptides 4.3 and D1 bound HLA-A*0201 molecules with high affinity;
- Peptides 4.3 and D1 stimulated CTL with a relatively limited TCR Vβ repertoire;
- In a longitudinal study, the CTL response to the variable D2 epitope diminished over time, while the response to the conserved epitope D1 stayed higher over time;

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gp160(121–129)	Env( )	KLTPLCVTL	HIV-1 infection	human(A2-supertype, A*0201)	[Altfeld (2001d)]

- Epitope name: Env-134. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)

- 2/22 individuals with chronic HIV-1 infection recognized this epitope in ELISPOT
- 0/12 acutely infected individuals recognized this epitope
- KLTPLCVTL binds to four HLA-A2 supertype alleles: A*0201, A*0202, A*0203 and A*6802 (highest affinity)

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gp160(121–129) gp120(120–128 LAI) KLTPLCVTL Vaccine human(A2) [Dupuis (1995)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- CTL from HLA-A2 positive subject react with this peptide

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gp160(121–129) gp120(120–128) KLTPLCVTL Vaccine human(A2) [Woodberry (1999)]

Vaccine: *Vector/type:* vaccinia *HIV component:* polyepitope

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested
- KLTPLCVTL was recognized by 3 of the patients

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gp160(121–129) gp120(120–128) KLTPLCVTL HIV-1 infection human(A2) [Kundu (1998b)]

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated
- KLTPLCVTL is a conserved HLA-A2 epitope included in this study – all six patients had this sequence as their HIV direct sequence, and a detectable CTL response
- CTL demonstrated against peptide-coated target, epitope is naturally processed and enhancible with vaccine

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gp160(121–129) gp120(120–128) KLTPLCVTL HIV-1 infection human(A2) [Kmieciak (1998b)]

- Increased CTL response to cells expressing a VV construct ΔV3 mutant compared with a full-length env gene product

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gp160(121–129) gp120(121–129) KLTPLCVSL *in vitro* stimulation human(A2) [Zarling (1999)]

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses

- Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL

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gp160(121–129) gp120(120–128) KTLPLCVTL HIV-1 infection human(A2) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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gp160(121–129) Env(134–142) KLTPLCVTL HIV-1 infection human(A2 supertype) [Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind four of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)

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gp160(121–129) Env( ) KLTPLCVTL Vaccine SJL/J HLA transgenic mice(A2.1) [Ishioka (1999)]

Vaccine: *Vector/type:* DNA *HIV component:* polyepitope

- A minigene vaccine construct encoding 6 HLA 2.1 and 3 HLA A11 restricted CTL epitopes, the universal Th cell epitope PADRE (pan-DR epitope) and an ER translocating signal sequence was constructed
- The epitopes were chosen for dominant recognition by CTLs during HBV and HIV infections in humans
- HLA transgenic mice were used for quantitating *in vivo* immunogenicity of DNA vaccines encoding HLA-restricted CTL epitopes – strong responses were observed to all nine epitopes, and CTL memory persisted up to four months after a single injection

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gp160(121–129) Env(120–128 clade B) KLTPLCVTL Vaccine human(A2.1) [Kundu (1998a)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- Ten HIV-1+ HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses

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gp160(156–165)	gp120(156–165)	NCSFNISTSI	HIV-1 infection	human(Cw*08)	[Ferris (1999)]

- Recognized by CTL clone LWF A5, isolated from a lab worker exposed to HIV-1 in 1985
- The processing of this epitope is TAP1/2-dependent, as are most Env epitopes, and it contains two N-linked glycosylation sites that are glycosylated in Env
- Only peptide that has been deglycosylated, a process that changes asparagine (N) to aspartic acid (D) was recognized: the aspartic acid at position 5 was critical, position 1 could be either D or N
- This peptide also contains a Cys involved in a disulfide linkage but reducing conditions did not effect recognition by CTL clone LWF A5
- The HIV-1 Env epitopes are typically processed by a TAP1/2 dependent mechanism, which involves cotranslational translocation into the ER, glycosylation, export back into the cytosol, and deglycosylation for processing, and retransport into the ER for the association with class I molecules
- The particular pathway of generating an epitope may have an impact on the presentation of that epitope, quantitatively as well as qualitatively

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gp160(156–165)	gp120(156–165 IIIB)	NCSFNISTSI	HIV-1 infection	human(Cw8)	[Sipsas (1997)]

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB
- NCSFNITTSI, a variant found in HIV-1 MN, was not recognized, thus this epitope was type-specific
- NCSFNISTSI contains two potential N-linked glycosylation sites and cysteine residue, possibly related to the requirement for a high sensitizing dose of peptide for CTL activity

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gp160(188–207)	gp120(193–212 BRU)	TTSYTLTSCNTSVITQA-CPK	HIV-1 infection	human(A2)	[Dadaglio (1991)]

- Defined through blocking CTL activity, and Env deletions

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gp160(191–200)	gp120(194–202 CM243 CRF01)	YRLINCNTSV	HIV-1 infection	human(A2)	[Sriwanthana (2001)]

- Epitope name: E191-200. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2

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gp160(191–200)	gp120(194–202 CM243 CRF01)	YRLINCNTSV	HIV-1 infection	human(A2)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested
- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by four amino acids, KLTSCNTSV
- This epitope was somewhat conserved in 4/8 subtypes: CRF01 (E), B, C, and D

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gp160(192–200)	gp120(192–199)	KLTSCNTSV	HIV-1 infection	human(A*02)	[Rinaldo (2000)]

- Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that persist after therapy and long periods of virus being below the level of detection

gp160(192–200)	gp120(192–199 HXB2R)	KLTSCNTSV	HIV-1 infection	human(A2)	[Brander (1995)]

- Epitope predicted on HLA binding motif, and studied in the context of inclusion in a synthetic vaccine

gp160(192–200)	gp120(192–199)	KLTSCNTSV	HIV-1 infection	human(A2)	[Huang (2000)]

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed
- Increases in γ interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-γ-production ELISPOT

gp160(192–200)	gp120(197–205)	TLTSCNTSV	Peptide-HLA interaction	human(A2)	[Garboczi (1992)]

- Crystallization of HLA-A2 molecules complexed with antigenic peptides – refers to Dadaglio *et al* 1991

gp160(192–200)	gp120(199–207)	TLTSCNTSV	HIV-1 infection	human(A2.1)	[Brander (1996)]

- This epitope was recognized by PBMC from 6/14 HIV+ asymptomatic patients
- This epitope was used along with pol CTL epitope ALQDSGLEV and a tetanus toxin T helper epitope for a synthetic vaccine
- This vaccine failed to induce a CTL response, although a helper response was evident

gp160(192–211)	gp120(199–219 SF2)	SLTSCNTSVITQACPK-VSFE	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160
- One of these 11 had CTL response to this peptide
- The responding subject was HLA-A2, -B21

gp160(201–225)	gp120(201–225 LAI)	ITQACPKVSFEPIPHYC-APAGFAI	Vaccine	human(CD4+ CTL)	[Johnson (1994b), Johnson (1994a)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- CD4+ CTL isolated from LAI IIIB gp160 vaccinees

gp160(202–221)	gp120(209–228)	TQACPKVSFEPIPIHYC-APA	*in vitro* stimulation	human( )	[Lieberman (1995)]

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide

gp160(202–221)	gp120( )	TQACPKVSFEPIPIHYC-APA	HIV-1 infection	human( )	[Weekes (1999b)]

- Almost all CD8+ T-cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed the CD28 depleted cell population
- HIV CTL responses to 3 Env and 2 Gag peptides were studied
- The clonal composition of TCR Vβ responses were studied and was found to be highly focused, with one TCR β-chain sequence tending to dominate the peptide-specific response – clones to this epitope were Vβ13.1

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gp160(202–221)	gp120( )	TQACPKVSFEPIPIHYC-APA	HIV-1 infection	human( )	[Weekes (1999a)]

- Epitope name: Peptide 740.18. Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28-CD8+ CTLp populations

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gp160(202–221)	gp120(209–228 SF2)	TQACPKVSFEPIPIHYC-APA	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160
- One of these 11 had CTL response to this peptide

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gp160(202–221)	gp120(209–228 SF2)	TQACPKVSFEPIPIHYC-APA	HIV-1 infection	human( )	[Lieberman (1997b)]

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients

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gp160(207–216)	gp120( )	KMTFEPIPIH	HIV-1 infection	human(A29)	[Cao (2000)]

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent-specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype
- CTL derived from subtype A clade infection (patient SP 528), recognized the subtype A version of the peptide (KMSFEPIPIH), had a slightly reduced specific lysis using the B clade version of the peptide (KVSFEPIPIH), and no lysis using the D clade version of the epitope (KVTFEPIPIH)
- Patient SP 528 is HLA A1, A29, B57, B81, Bw4, Bw6

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gp160(208–217)	gp120( )	VSFEPIPIHY	HIV-1 exposed seronegative	human(A29)	[Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells

- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women

gp160(208–217)	gp120(263–272)	VSFEPIPHY	HIV-1 exposed seronegative, HIV-1 infection	human(A29)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

gp160(209–217)	( )	SFEPIPIHY		(A29)	[Altfeld(2000), Brander & Goulder(2001)]

gp160(209–217)	gp120(213–221 SF2)	SFEPIPIHY	HIV-1 infection	human(A29)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A29+ individuals that had a CTL response to this epitope broken down by group: 1/3 group 1, 0/0 group 2, and 0/0 group 3

gp160(212–231)	gp120( )	PIPIHYCAPAGFAILKC-NNK	HIV-1 infection	human( )	[Weekes (1999a)]

- Epitope name: Peptide 740.19. Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28-CD8+ CTLp populations

gp160(212–231)	gp120(219–238 HXB2)	PIPIHYCAPAGFAILKC-NNK	HIV-1 infection	human( )	[Lieberman (1992)]

- CTL epitope defined by T-cell line and peptide mapping

gp160(212–231)	gp120(219–238)	PIPIHYCAPAGFAILKC-NNK	*in vitro* stimulation	human( )	[Lieberman (1995)]

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide

gp160(212–231)	gp120( )	PIPIHYCAPAGFAILKC-NNK	HIV-1 infection	human(A2)	[Weekes (1999b)]

- Almost all CD8+ T-cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed in the CD28 depleted cell population
- HIV CTL responses to 3 Env and 2 Gag peptides were studied

- The clonal composition of TCR Vβ responses was studied and was found to be highly focused, with one TCR β-chain sequence tending to dominate the peptide-specific response – clones to this epitope were Vβ13.6

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gp160(212–231) gp120( ) PIPIHYCAPAGFAILKC-NNK HIV-1 infection human(B57) [Jin (1998b)]

- Progressive HIV-1 infection and CD4 decline was associated decreased the IL-2-expandable HIV-1 CTL response in 10 asymptomatic HIV-infected patients – this observation may be partially due to a reduction and impaired function of T helper cells, CTL exhaustion and APC dysfunction
- Continued presence of HIV-1 specific memory cells (CTLp) was observed in three patients, one to GIWGCSGKLICTTAV, one to ALIWEDLRSLCLFSY, and one to PIPIHYCAPAGFAILKCNNK

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gp160(237–246) Env( ) GPCKNVSTVQ human(B56) [De Groot (2001)]

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay
- GPCKNVSTVQ was newly-defined as an epitope in this study, was shown to stimulate an ELISPOT response, and to bind to HLA-B7

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gp160(239–247) gp120(241–249 LAI) CTNVSTVQC HIV-1 infection human(Cw8) [Sipsas (1997)]

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB
- CTNVSTVQC contains a potential N-linked glycosylation site and cysteine residues, possibly related to a requirement for a high sensitizing dose of peptide for CTL activity

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gp160(242–261) gp120(249–268) VSTVQCTHGIRPVVST-QLLL *in vitro* stimulation human( ) [Lieberman (1995)]

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide

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gp160(242–261) gp120(249–268 SF2) VSTVQCTHGIRPVVST-QLLL HIV-1 infection human( ) [Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160
- One of these 11 had CTL response to this peptide
- The responding subject was HLA-2, -B21

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gp160(242–261) gp120(249–268) VSTVQCTHGIRPVVST-QLLL HIV-1 infection human( ) [Lieberman (1997b)]

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients

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gp160(252–260) gp120(255–263 SF2) RPIVSTQLL HIV-1 infection human(B*3501) [Tomiyama (1997)]

- A CTL clone responsive to this epitope was obtained

- Only 1/7 B35-positive individuals had a CTL response to this epitope
- An I to V substitution at position 3 reduces specific lysis, but not binding to B*3501
- A Q to H substitution at position 7 abrogates specific lysis, but not binding to B*3501

gp160(252–260)	gp120(255–263 SF2)	RPIVSTQLL	HIV-1 infection	human(B35)	[Shiga (1996)]

- Binds HLA-B*3501

gp160(252–260)	( )	RPIVSTQLL	HIV-1 infection	human(B35)	[Kawana (1999)]

- HLA B35 is associated with rapid disease progression
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation

gp160(252–261)	Env( )	RPVVSTQLLL		human(B7)	[De Groot (2001)]

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 of the predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay
- RPVVSTQLLL was one of the 15, and had been previously identified as an HLA-B7 epitope, and was confirmed in this study

gp160(252–271)	gp120(256–275 LAI)	RPVVSTQLLLNGSLAE-EEVV	HIV-1 infection	human(B7)	[Shankar (1996)]
gp160(291–307)	gp120(295–312 BRU)	SVEINCTRPNNNTRKSI	HIV-1 infection	human(A2)	[Dadaglio (1991)]

- Defined through blocking CTL activity, and Env deletions

gp160(297–322)	gp120(297–322 IIIB)	TRPNNNTRKRIRIQRG-PGRAFVTIGK	Vaccine	murine(H-2D^d)	[Chang (1999)]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* V3 *Stimulatory Agents:* liposome

- Induction of peptide-specific CTLs in BALB/c mice was dependent on immunization with peptide encapsulated liposomes containing MPL as adjuvant
- T26K (26mer) elicited a stronger AB and CTL response than R15K (a V3 15mer, RIQRGPGRAFVTIGK)

gp160(297–330)	Env(303–335 BX08)	TRPNNNTRKSIHIGPG-RAFYATGEIIGDIRQAH	Vaccine	human( )	[Gahery-Segard (2000)]

Vaccine: *Vector/type:* lipopeptide *HIV component:* six peptides

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial

- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 6/10 reacted to this peptide
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in five vaccinees
- None of the 12 tested had an IgG response to gp120 or gp160 and vaccinees could be differentiated from HIV-1 seropositive individuals with a commercial HIV detection kit – no neutralizing antibodies were observed

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gp160(298–307)	gp120(298–307)	RPNNNTRKSI	HIV-1 infection	human(B*07)	[Ferris (1999), Hammond (1995)]

- The processing of this epitope is TAP1/2-dependent, as are most Env epitopes, and it contains an N-linked glycosylation site that is glycosylated in Env
- Peptide that had been deglycosylated, a process that changes asparagine (N) to aspartic acid (D) (RPNDNTRKSI) was recognized a 100-fold more efficiently than either glycosylated or non-glycosylated RPNNNTRKSI
- Position 5 is not involved with HLA B*07 binding, so is probably important for TCR recognition
- HIV-1 Env epitopes are typically processed by a TAP1/2 dependent mechanism, which involves cotranslational translocation into the ER, glycosylation, export back into the cytosol, and deglycosylation for processing, and retransport into the ER for the association with class I molecules
- The particular pathway of generating an epitope may have an impact on the presentation of that epitope, quantitatively as well as qualitatively

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gp160(298–307)	gp120(302–312 HXB2)	RPNNNTRKSI	HIV-1 infection	human(B*0702)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*0702 epitope

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gp160(298–307)	gp120(302–312 HXB2)	RPNNNTRKSI	HIV-1 infection	human(B7)	[Safrit (1994b)]

- CTL from two acute seroconversion cases

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gp160(298–307)	gp120(302–312 HXB2)	RPNNNTRKSI	HIV-1 infection	human(B7)	[Hammond (1995)]

- Peptide processed by a TAP-1/2-dependent pathway only
- CTL from an acute seroconverter

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gp160(298–307)	gp120(302–312 HXB2)	RPNNNTRKSI	HIV-1 infection	human(B7)	[Wolinsky (1996)]

- Longitudinal study of epitope variation *in vivo*

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gp160(298–307)	gp120(302–311 clade B)	RPNNNTRKSI	HIV-1 infection	human(B7)	[Wilson (1998b)]

- The extent of CTL interclade cross-reactivity from CTL isolated from individuals newly infected with B clade virus was studied, and extensive cross-reactivity was observed

- Two HLA B7 individuals had CTL response to B_LAI, A_92UG037 and C_92BR025 gp160, but were B clade strain MN non-responders – the authors note that the B7 epitope RPNNNTRKSI is immunodominant, conserved between the LAI and clade A and C strains, but is very divergent in MN (RPNYNKRKRI), and that this epitope might be dominating the specificity of the response in the HLA B7 individuals

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gp160(298–307) gp120(303–312 SF2) RPNNNTRKSI HIV-1 infection human(B7) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 1/3 group 2, and 1/1 group 3

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gp160(298–307) gp120(298–307) RPNNNTRKSI HIV-1 infection human(B7) [Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope

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gp160(298–307) gp120(303–312 IIIB) RPNNNTRKSI HIV-1 infection human(B7?) [Wilson (1996)]

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study
- RPNNNTRKDI and RPNNNTRKGI, naturally occurring variants, were found in non-transmitting mother – ability to recognize these variants was not determined

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gp160(303–322) gp120( ) TRKSIHIGPGRAFYTT-GE Vaccine murine BALB/c( ) [Luo (1998)]

Vaccine: *Vector/type:* virus-like particle *Strain:* B subtype consensus *HIV component:* gag, V3

- Intramuscular injection of chimeric gag-env virus-like particles (VLPs) containing V3 loop sequences into BALB/c mice induce V3 specific CTL – TRKSIHIGPGRAFYTTGE is a B subtype consensus that stimulated a cross-reactive CTL response

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gp160(304–318) gp120(304–318 IIIB) RKSIRIQRGPGRAFV Vaccine murine(H-2^d) [Kang (1999)]

Vaccine: *Vector/type:* virus-like particle *Strain:* HIV-2 VLP, MN, IIIB, RF, SF2 *HIV component:* gag, V3

- Virus-like particles could be formed from HIV-2 gag after deleting 143 amino acids at the C-terminal end – a proline rich region in positions 373-377 was critical to VLP formation
- CTL responses in BALB/c mice were induced by chimeric gag-V3 particles against the V3 region of HIV-1 clade B isolates IIIB (SIRIQRGRAFVTI), MN (KRIHIGPGRAFYTTK), RF (SITKGPGRVIYATGQ), and SF2 (SIYIGPGRAFHTTGR)
- The vaccine induced CTL were cross-reactive with a broad spectrum of B clade isolates, with the exception of the RF V3 which did not induce CTL

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gp160(308–322) gp160( ) RIHIGPGRAFYTTKN Vaccine human( ) [Pinto (1999)]

Vaccine: *Vector/type:* peptide *Strain:* MN *HIV component:* V3 *Stimulatory Agents:* Montanide ISA 51

- Epitope name: Peptide P18. Eight HIV+ individuals were vaccinated with peptides containing specific T helper, CTL and Ab epitopes in Montanide ISA 51 in a Phase I trial
- Four displayed a 4-fold increase in PCLUS 3-18 MN-specific T helper responses
- One patient developed a new, sustained P18MN-peptide-specific CTL response – the patient's HLA haplotype was A2,30; B53,7; Cw2,4, and anti-HLA A2 antibody did not inhibit the response, suggesting it was not A2
- Patients with low baseline Ab levels developed an increase of neutralizing Ab titers
- No significant change was observed in plasma HIV viral loads and CD4 cell counts

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gp160(308–322) gp120( ) RIHIGPGRAFYTTKN HIV-1 infection chimpanzee( ) [Lubeck (1997)]

- Epitope-specific CTL detected in chimpanzees immunized with adenovirus-HIV-1 MN gp160 recombinant
- CTL response may account for protection against subsequent HIV-1 SF2 challenge in a chimpanzee lacking neutralizing antibodies

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gp160(308–322) gp120(315–329 IIIB) RIQRGPGRAFVTIGK HIV-1 exposed seronegative human( ) [Pinto (1995)]

- CTL and T helper cell reactivity in healthcare workers exposed to HIV

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gp160(308–322) gp120(313–327 MN) RIHIGPGRAFYTTKN HIV-1 exposed seronegative human( ) [Pinto (1995)]

- CTL and T helper cell reactivity in healthcare workers exposed to HIV

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gp160(308–322) gp120(315–329 IIIB) RIQRGPGRAFVTIGK Vaccine human(A11) [Achour (1994)]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- One of 3 HLA type restrictions associated with this peptide

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gp160(308–322) gp120(315–329 BRU) RIQRGPGRAFVTIGK HIV-1 infection human(A2) [Dadaglio (1991)]

- Defined through blocking CTL activity, and Env deletions

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gp160(308–322) gp120(315–329 IIIB) RIQRGPGRAFVTIGK HIV-1 infection human(A2) [Clerici (1991)]

- Helper and cytotoxic T-cells can be stimulated by this peptide (P18)

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	human(A2, A3)	[Achour (1993)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- Two of 3 HLA type restrictions associated with this peptide

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	murine(D^d)	[Takahashi (1989a)]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* V3

- R(8) F(10) MHC/peptide interaction

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	murine(D^d)	[Sastry (1992)]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* V3

- Free peptide injected into the footpad of a mouse could stimulate specific CTL

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	murine(D^d)	[Ahlers (1997b)]

Vaccine: *Vector/type:* peptide *Strain:* MN *HIV component:* V3

- PCLUS 3-18MN synthetic peptide vaccine construct contained T1 helper epitope covalently linked to truncated P18 CTL epitope
- A substitution in the T1 peptide stimulated an enhanced Th response and class II binding specificity, which in turn enhanced CTL induction by vaccine
- Construct PCLUS 3-18MN is currently in a phase I vaccine clinical trial

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gp160(308–322)	gp120(313–327 MN)	RIHIGPGRAFYTTKN	Vaccine	murine(D^d)	[Takahashi (1989b)]

Vaccine: *Vector/type:* vaccinia *Strain:* MN, IIIB *HIV component:* gp160

- Y(11 MN) exchange with V(11 IIIB) interchanges specificities

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gp160(308–322)	gp120(313–327 IIIB MN RF)	SITKGPGRVIYATGQ	Vaccine	murine(D^d)	[Takahashi (1992)]

Vaccine: *Vector/type:* vaccinia *Strain:* RF *HIV component:* gp160

- Comparison of MN, IIIB, and RF specificities, position 11 is critical

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gp160(308–322)	gp120( )	RIQRGPGRAFVTIGK	Vaccine	murine(H-2^d)	[Deml (1997)]

Vaccine: *Vector/type:* virus-like particle *HIV component:* Gag, Env

- Env bound to virus-like particles (VLPs) can elicit a CTL response that is dependent on the amount of Env presented on the VLP

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gp160(308–322)	gp120(313–327 MN)	RIHIGPGRAFYTTKN	Vaccine	murine BALB/c(H-2^d)	[Fomsgaard (1998a)]

Vaccine: *Vector/type:* DNA *Strain:* MN *HIV component:* gp160, V3

- Enhanced B and CTL responses to the V3 region occur following epidermal immunization by gene gun with a chimeric DNA vaccine of V3-hepatitis B surface antigen relative to a gp160 plasmid vaccine

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gp160(308–322)	gp120(313–327 MN)	RIHIGPGRAFYTTKN	Vaccine	murine BALB/c(H-2^d)	[Ahlers (1996), Ahlers (1997a)]

Vaccine: *Vector/type:* peptide *Strain:* MN *HIV component:* V3 *Stimulatory Agents:* GMCSF, IL-12

- Vaccine constructs containing helper, antibody and CTL peptide epitopes induce strong Th1, CTL and NAb responses against the autologous HIV-1 virus
- The peptide CTL response was as cross-reactive as one elicited by a vaccinia construct expressing rgp160 MN
- GM-CSF and IL-12 were the two cytokines most effective for inducing and boosting CTLs

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	murine(H-2^d)	[Layton (1993)]

Vaccine: *Vector/type:* virus-like particle *Strain:* IIIB *HIV component:* V3, Gag

- V3-Ty-Virus-like particles can induce type-specific CTL in mice in the absence of adjuvant

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	murine(H-$2^{d,p,u,q}$)	[Shirai (1992), Shirai (1993)]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- Epitope name: P18. In a murine system multiple class I molecules can present this peptide to CTL, including H-2D^d, H-2D^p, H-2D^q, H-2L^q
- The MHC class I molecule D^d as well as H-$2^{u,p,q}$, were found to present peptides P18 and HP53
- The V-β usage in T-cells showing cross-reaction between these two peptides was conserved for H-$2^{d,u,p}$, but not in H-2^q

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gp160(308–322)	gp160( )	GIHIGPGRAFYAARK	Vaccine	murine(H-2D^d)	[Morris (2000)]

Vaccine: *Vector/type:* recombinant protein, peptide *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* mucosal adjuvant LT(R192G)

- LT(R192G) induces gp160-specific serum and mucosal IgG1 and IgG2a, systemic CTL activity and Th1 and Th2 cytokine responses upon internasal immunization

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	murine(H-2D^d)	[Porgador (1997)]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* V3 *Stimulatory Agents:* cholera toxin adjuvant

- A intranasal peptide vaccine with cholera toxin as a mucosal adjuvant was given.
- IIIB peptide referred to as R15K
- Peptide-specific CTLs were induced after *in vitro* restimulation with peptide-pulsed targets
- R15K was superior at inducing CTL compared to the RGPGRAFVTI, in contrast to the findings of Nehete *et al*.
- Memory CTL responses were induced

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	(H-2D^d)	[Chiba (1999)]

Vaccine: *Vector/type:* vaccinia with H1 influenza HA gene cassette *Strain:* IIIB *HIV component:* P18

- Epitope name: P18. Vaccine was capable of priming P18IIIB specific CTL in BALB/c mice, but could not induce a P18IIIB-specific antibody response

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gp160(308–322)	gp120( )	RIHIGPGRAFYTTKN	Vaccine	murine(H-2D^d)	[Casement (1995)]

Vaccine: *Vector/type:* peptide *Strain:* MN, SC *HIV component:* V3

- Epitope name: P18. V3 peptides from MN and SC induce murine CTL that are cross-reactive with diverse strains

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gp160(308–322)	gp120(313–327 MN)	RIHIGPGRAFYTTKN	Vaccine	murine(H-2D^d)	[Newman (1997)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp120 *Stimulatory Agents:* QS-21 adjuvant

- Epitope name: P18. MN vaccine induced CTL reactive with MN, IIIB and RF vaccinia-expressed Env, but not this peptide

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	murine(H-2D^d)	[Newman (1997)]

Vaccine: *Vector/type:* recombinant protein *Strain:* IIIB *HIV component:* gp120 *Stimulatory Agents:* QS-21 adjuvant

- Epitope name: P18. IIIB vaccine induced IIIB type-specific CTL to this peptide (P18), and an additional Env CTL response that was cross-reactive

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gp160(308–322)	gp120(315–329)	RIQRGPGRAFVTIGK	Vaccine	murine(H-2D^d)	[Takahashi (1988)]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- Epitope name: P18. V3 loop CTL response in mice vaccinated with gp160

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gp160(308–322)	gp120(315–329)	RIQRGPGRAFVTIGK	Vaccine	murine BALB/c(H-2D^d)	[Fukasawa (1998)]

Vaccine: *Vector/type:* liposome *Strain:* IIIB *HIV component:* V3 *Stimulatory Agents:* oligomannose

- Epitope name: P18. The peptide RIQRGPGRAFVTIGK was incorporated into liposomes and given as a subcutaneous injection, which induces a MHC class I restricted CTL response in mice
- Liposomes coated with oligomannose show no toxicity and can elicit a potent CTL response upon a single subcutaneous infection, while non-coated liposomes do not, suggesting that oligomannose may be a good adjuvant for CTL responses

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gp160(308–322)	gp120(315–329 IIIB)	RIQRGPGRAFVTIGK	Vaccine	murine(H-2D^{d,p,q}, H-2^u)	[Shirai (1996)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- Epitope name: P18. Multiple murine MHC can cross-present this epitope (P18) and HP53, DRVIEVVQGAYRAIR, to specific CTL

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gp160(308–322)	gp120( )	RIQRGPGRAFVTIGK	Vaccine	murine(H-2^d)	[Griffiths (1993)]

Vaccine: *Vector/type:* recombinant protein *HIV component:* Gag, V3

- Gag-V3 fusion protein immunization elicited V3 CTL response in mice

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gp160(308–322)	gp120( )	RIQRGPGRAFVTIGK	Vaccine	murine(H-2^d)	[Barouch (1998)]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* gp120 *Stimulatory Agents:* IL-2 or IL-2/Ig

- Epitope name: P18. A discistronic IL-2 gp120 expression vector gave a weaker CTL response than gp120 alone in the expression vector, however co-administration of an Il-2/IgG fusion protein enhanced the immune response and administration of a Il-2/IgG plasmid had a response that depended on the timing of administration.
- This study showed that a response to an HIV-1 DNA vaccine could be either augmented or suppressed by plasmid Cytokine/Ig administration

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gp160(308–322)	Env(308–322 IIIB)	RIQRGPGRAFVTIGK	Vaccine	murine(H-2^d)	[Uno-Furuta (2001)]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* V3 loop *Stimulatory Agents: in vivo* electroporation, immunostimulatory sequence ISS, B7-1

- Epitope name: P18. Peptide immunization usually doesn't elicit a good CTL response because epitopes are not internalized and processed and presented, so vaccination with electric pulsing was tried (i.m. injection followed by 8 electric pulses), to enhance peptide uptake through electroporation
- BALB/c immunized with HIV P18 or hepatitis C P17 peptides with an electric pulse elicited a CTL response, those that did not receive the pulse did not
- The CTL response was enhanced by addition of immunostimulatory sequences ISS in the plasmid pCMV-LacZ, that contains hexamers GACGTC, AGCGCT, AACGCT, sequences common in prokaryotic genomes but rare in eukaryotic genomes that elicit Th1 cytokines and result in B cell and T-cell proliferation
- The CTL response was also enhanced by addition of B7-1 cDNA – the B7 family of proteins transduce co-stimulatory signals through interaction with CD28

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gp160(308–322)	gp160( )	RIHIGPGRAFYTTKN	Vaccine	murine BALB/c and C57/BL6(H-2^d and H-2^b)	[Fomsgaard (1998b)]

Vaccine: *Vector/type:* DNA *Strain:* MN *HIV component:* gp160

- CTL responses to a primary gene gun vaccination were rapid and strong for several methods of vaccinations: i.m., bupivacaine pretreatment, cardiotoxin pretreatment or gene gun – the CTL response was more rapid and consistent than the antibody response

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gp160(309–317)	gp120(310–318 SF2)	IYIGPGRAF	HIV-1 infection	human(A*2402)	[Ikeda-Moore (1997)]

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402
- This peptide induced CTL in 1/4 HIV-1+ people tested
- IYIGPGRAF bound to A*2402 strongly, the epitope can be processed in a vaccinia construct and presented – no specific CTL clones were obtained

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gp160(309–318)	gp120(314–323 CM243 CRF01)	ITVGPGQVFY	HIV-1 infection	human(A11)	[Sriwanthana (2001)]

- Epitope name: E309-318. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was strongly reactive in HIV+ control study subject 184 who carried HLA-A11

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gp160(309–318) gp120(314–323 CM243 CRF01) ITVGPGQVFY HIV-1 infection human(A11) [Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it
- This epitope was not conserved in other subtypes, and exact matches were rare

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gp160(310–318) Env(313–321) HIGPGRAFY HIV-1 infection human(A*3002) [Mulligan (2001)]

- Epitope name: E30. CTL response in Patient 07107 with HLA genotypes A*3002, A*3201, B*4501, B*5301, Cw*0401, Cw*1202

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gp160(310–323) gp120(315–328 MN) HIGPGRAFYTTKNI Vaccine murine(H-2D^d) [Arp (1999)]

Vaccine: *Vector/type:* canarypox prime with pseudovirion boost *Strain:* MN, IIIB *HIV component:* gp120, Gag, Pro

- Epitope name: p97. The vaccine vCP205, canarypox vector, MN gp120 + Gag/Pro IIIB, with an HIV-1 pseudovirion boost was given to mice;)
- HIV-1 pseudovirion boost enhanced the CTL response to this epitope in immunized BALB/c mice as measured by CTL lysis and IFNγ production

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gp160(311–319) gp120(312–320 SF2) IGPGRAFHT Vaccine murine(D^d) [Selby (1997)]

Vaccine: *Vector/type:* DNA *Strain:* SF2 *HIV component:* gp120

- Murine CTL response to peptide was observed after immunization with DNA plasmid containing HIV-1 (SF2) gp120 gene regulated by bacteriophage T7 promoter
- CTL response required coadministration of rec vaccinia virus expressing T7 RNA polymerase or T7 RNA polymerase soluble protein

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gp160(311–319) gp120( ) IGPGRAFHT Vaccine murine(H-2D^d) [Barnett (1997)]

Vaccine: *Vector/type:* DNA prime with rgp120 boost *Strain:* SF2 *HIV component:* gp120

- CTL were induced by vaccine, and restimulated *in vitro* with V3 peptide
- DNA vaccine with protein boost stimulated both CTL and antibodies
- Strains SF2 (IGPGRAFHT), US4 (IGPGRAFYA), and CM235 (IGPGQVFYR) were tested

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gp160(311–320) gp160(318–327 IIIB) RGPGRAFVTI Vaccine Macaca fuscata( ) [Okuda (1997)]

Vaccine: *Vector/type:* DNA prime with peptide boost *Strain:* IIIB *HIV component:* gp160, V3, CD4BS, HPG30

- Epitope name: P18. Murine BALB/c (H-2^d) and macaque both showed highest level of CTL vaccine response when a DNA vaccine was boosted with a peptide including four peptide subtypes of the V3 region, HPG-30 and a fragment of the CD4 binding region

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gp160(311–320) gp120(318–327) RGPGRAFVTI HIV-1 infection human( ) [Kmieciak (1998b)]

- Epitope name: P18. Increased CTL response to cells expressing a VV construct ΔV3 mutant compared with a full-length env gene product
- This epitope doesn't have A2 anchors, but has features that confer promiscuous A2 binding, which may relate to the inhibitory effect seen in this paper

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gp160(311–320) Env( ) RGPGRAFVTI Vaccine murine BALB/c( ) [Lu (1999)]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* gp160, rev *Stimulatory Agents:* MIP-1α

- Epitope name: P18. MIP-1α co-inoculation increased IgG1/IgG2a ratio T-helper type 1 response.
- A MIP-1αexpression plasmid increased the CTL response to this DNA vaccine, as well as the T help response, presumably by the MIP-1αinteracting with T lymphocytes and macrophages

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gp160(311–320) gp160(318–327 IIIB) RGPGRAFVTI *in vitro* stimulation human(A*0201) [Alexander-Miller (1996)]

- Epitope name: P18. This eptiope stimulates a CTL line derived from an HIV negative donor.
- This immunogenic peptide does not have the known binding motif for A2.1
- The same optimal peptide for this human HLA-A2.1 epitope was observed for a murine H-2 D^d epitope

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gp160(311–320) gp120(311–320 IIIB) RGPGRAFVTI human(A*0201) [Brander & Goulder(2001)]

- Epitope name: P18. C. Brander notes this is an A*0201 epitope

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gp160(311–320) gp160(318–327 IIIB) RGPGRAFVTI Vaccine human(A2) [Achour (1996)]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- Epitope name: P18. Individual was immunized with rec vaccinia gp160 IIIB and boosted with purified gp160
- Lysis only occurs with IIIB P18 peptide pulsed onto autologous targets; MN, RF, SIMI P18 peptides fail to stimulate CTL
- Restimulating immune cells from gp160 IIIB vaccinees with MN, RF, or SIMI P18 did not enhance the MN, RF, or SIMI specific CTL response

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gp160(311–320) gp160(318–327 SIMI) MGPKRAFYAT Vaccine human(A2) [Achour (1996)]

Vaccine: *Vector/type:* vaccinia prime with rgp160 boost *Strain:* SIMI *HIV component:* gp160

- Epitope name: P18. Individual was immunized with rec vaccinia gp160 SIMI and boosted with purified recombinant gp160 SIMI
- P18 MN and RF peptides were able to stimulate the HIV-specific CTL that arose in response to the SIMI vaccination, thus the P18 MN peptide (IGPGRAFYTT) and the P18 RF peptide (KGPGRVIYAT) could cross-react

- The P18 IIIB peptide does not cross-react (RGPGRAFVTI in the epitope region)
- gp160 SIMI primed immune cells could generate a significantly broader specificity when stimulated with P18 MN or P18RF peptides, but not P18 IIIB

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gp160(311–320) gp120(311–320) RGPGRAFVTI HIV-1 infection human(A2) [Day (2001)]

- Epitope name: P18. The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person

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gp160(311–320) gp160(318–327 IIIB) RGPGRAFVTI Vaccine murine(D) [Nehete (1995)]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* V3 *Stimulatory Agents:* Freund's adjuvant

- Epitope name: P18. RGPGRAFVTI was defined as the optimal peptide for vaccination, out of RIQRGPGRAFVTIGK
- This peptide, in a carrier-free form in Freund's adjuvant, could stimulate Env specific CTL in BALB/c mice

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gp160(311–320) gp160(318–327 IIIB) RGPGRAFVTI Vaccine murine(D^d) [Takahashi (1993)]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* V3

- Epitope name: P18. Successful priming with vaccination of peptide pulsed splenic dendritic cells

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gp160(311–320) gp160(318–327 IIIB) RGPGRAFVTI Vaccine murine(D^d) [Takahashi (1996)]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* V3

- Epitope name: P18. Exposure of CD8+ CTL to free peptide corresponding to the epitope results in strong inhibition of the CTL response to targets presensitized with the same peptide
- The authors propose this is due to a "self-veto", where the CTL is inactivated by a CD8+ cell carrying the appropriate peptide-MHC complex

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gp160(311–320) Env(318–327) RGPGRAFVTI murine(H-2^d) [Lopez (2000)]

- Epitope name: P18. A series of protease and proteasome inhibitors was used to identify elements of the processing pathway of this epitope, called p18, both from within Env and from within a chimeric hepatitis B protein which allows proper processing
- Lactacystin, a proteasome inhibitor, partially inhibits endogenous processing of p18 epitope suggesting both a proteasome pathway and an additional pathway can be used
- Both TAP dependent and TAP-independent pathways can be used
- 1,10-phenanthrolin (metallopeptidases inhibitor) blocks epitope presentation demonstrating metalloproteinase processing in the Tap-dependent pathway
- The Tap-independent pathway does not involve processing by metalloproteinases
- This epitope is immunodominant in mice, and is presented by multiple human HLA alleles – it as been suggested that the high processing efficiency of this epitope might result in poor presentation of co-expressed epitopes

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gp160(311–320)	gp120( )	RGPGRAFVTI	Vaccine	murine(H-2^d)	[Hanke (1998a), Hanke (1998b)]

Vaccine: *Vector/type:* vaccinia *HIV component:* polyepitope

- Epitope name: P18. This murine epitope was incorporated into a vaccine of CTL epitopes expressed together including 20 HIV epitopes recognized by humans from 12 HLA types, one murine HIV epitope and three macaque HIV epitopes, delivered in a vaccinia virus Ankara (VVA) construct
- The murine vaccination was more effective at generating CTL when given i.v. rather than i.m.

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gp160(311–320)	gp160(318–327 IIIB)	RGPGRAFVTI	Vaccine	murine BALB/c(H-2^d)	[Hamajima (1997)]

Vaccine: *Vector/type:* peptide *HIV component:* V3, HPG30, CD4BS *Stimulatory Agents:* IL-12

- Epitope name: P18. B cell epitope HGP-30 also serves as a CTL epitope
- Vaccine combined HGP-30, V3 loop peptide variants, and CD4 binding site peptide
- IL-12 expression plasmid included with the vaccination enhanced the CTL response

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gp160(311–320)	gp160(318–327 IIIB)	RGPGRAFVTI	Vaccine	murine(H-2^d)	[Arai (2000)]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* 8 Br-cAMP/CMV promotor

- Epitope name: P18. Low-dosage 8 Br-cAMP given in combination with a DNA vaccine to BALB/c mice increased IgG and sIgA levels, and enhanced Th1, Th2 and CTL activity – the adjuvant activity may be mediated by activation of the CMV promotor in the DNA vaccine

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gp160(311–320)	gp120(318–327 IIIB)	RGPGRAFVTI	Vaccine	murine(H-2^d)	[Goletz (1997)]

Vaccine: *Vector/type:* fusion protein with anthrax delivery domain *HIV component:* gp120

- Epitope name: P18. Anthrax lethal toxin can deliver proteins to the cytosol of eukaryotic cells
- A fusion protein linking the delivery domain of the anthrax protein to gp120 achieved cellular uptake, and gp120 was processed allowing presentation of this V3 epitope to CTL *in vitro*

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gp160(311–320)	gp120(318–327 IIIB)	RGPGRAFVTI	Vaccine	murine(H-$2^{d,p,u}$)	[Shirai (1997)]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- Epitope name: P18. Three class I MHC, H-$2^{d,p,u}$, that differ in sequence and serology, cross-present this peptide to T-cells of each of the other haplotypes
- The amino acids R, F, and I are each critical for strong CTL activity with all three MHC molecules

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gp160(311–320)	gp160( )	RGPGRAFVTI	Vaccine	murine(H-2^{d17})	[Hanke (1998a)]

Vaccine: *Vector/type:* vaccinia *HIV component:* polyepitope

- Epitope name: P18. Recombinant modified vaccinia virus Ankara (MVA) is an attenuated vaccinia that can not replicate in mammalian cells – strings of CTL epitopes were delivered and expressed in a MVA DNA vector

- γ IFN and CTL activity were induced after a single vaccination
- An MVA boost enhanced the response

gp160(311–320)	Env( )	IGPGRARYAR	Vaccine	murine BALB/c(H-2D)	[Belyakov (1998b)]

Vaccine: *Vector/type:* vaccinia *Strain:* 89.6 *HIV component:* gp160

- Epitope name: P18. Recombinant modified vaccinia virus Ankara (MVA), an attenuated vaccina which has lost the ability to replicate in mammalian cells, was used as the live vector for this vaccine study
- A single intrarectal mucosal immunization resulted in long lasting mucosal CTL responses and production of proinflammatory cytokines in mucosal sites, indicating that MVA was as effective in inducing mucosal CTL as replicating recombinant vaccinia

gp160(311–320)	Env( )	IGPGRARYAR	Vaccine	murine BALB/c(H-2D)	[Belyakov (1998a)]

Vaccine: *Vector/type:* peptide *Strain:* IIIB *HIV component:* V3

- Epitope name: P18. HIV protection and mucosal CTL response was studied – an HIV peptide immunogen could protect against gp160 expressing vaccinia in a murine intrarectal challenge system in which neutralizing Abs did not play a role, demonstrating mucosal CTL at the site of exposure can be protective

gp160(311–320)	gp120( )	IGPGRAFYTT	Vaccine	murine(H-2D^d)	[Lapham (1996)]

Vaccine: *Vector/type:* B. abortus-peptide conjugate

- Epitope name: P18. *B. abortus*-peptide conjugate induced a virus-specific CTL response in CD4+ lymphocyte depleted mice

gp160(311–320)	gp160( )	RGPGRAFVTI	Vaccine	murine(H-2D^d)	[Bruce (1999)]

Vaccine: *Vector/type:* non-replicating adenovirus *Strain:* IIIB *HIV component:* Env, Rev

- Epitope name: P18. A good HIV-1 Env immune response using non-replicating adenovirus vectors in BALB/c mice is dependent upon the presence of the stimulatory tat/rev 5'splice-donor site sequence and the presence of Rev
- Administration of monocistronic RAd501 expressing env and RAd46 expressing rev resulted in a positive CTL response, but required two immunizations for a CTL response comparable to that induced by the bicistronic virus RAd142
- Administration of RAd501 alone gave a low CTL response, but no humoral response, suggesting a lower level of antigen may be required to stimulate CTL

gp160(311–320)	gp120( )	IGPGRAFYTT	Vaccine	murine(H-2D^d)	[Lapham (1996)]

Vaccine: *Vector/type:* B. abortus-peptide conjugate

- Epitope name: P18. *B. abortus*-peptide conjugate induced a virus-specific CTL response in CD4+ lymphocyte depleted mice

gp160(311–320)	gp160(318–327 IIIB)	RGPGRAFVTI	Peptide-HLA interaction	murine(H-2D^d)	[Takeshita (1995)]

- Epitope name: P18. XGPXRXXXXI are critical for binding, consistent with H-2D^d motif XGPX(RKH)XXX(X)(LIF)

gp160(311–320)	Env( )	RGPGRAFTVTI	Vaccine	murine(H-2D^d)	[Hanke & McMichael(1999), Hanke (1999)]

Vaccine: *Vector/type:* DNA/MVA boost *HIV component:* V3

- Epitope name: P18. Vaccinated mice elicited a CTL response to a gene gun-delivered multiepitope vaccine to two epitopes studied that are known to elicit CTL in mice: SYIPSAEKI from Plasmodium berghei and RGPGRAFTVTI from HIV-1 Env
- Different vaccination protocols were tested and it was found that a gene gun mediated delivery followed by an MVA boost was as good as i. m. immunization followed by a MVA boost – this is advantageous as gene gun delivery requires far less DNA than i.m. DNA priming
- CTL activity was high (60% - 70% specific lysis at effector target) when vaccinated with a single gene gun immunization and an MVA boost, and improved with two gene gun vaccinations

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gp160(311–320)	Env( )	RGPGRAFVTI	*in vitro* stimulation	murine(H-2Dd)	[Nakagawa (2000)]

- Epitope name: I-10. The CTL line LINE-IIIB was generated by repetitive restimulation of BALB/c spleen cells with vSC-25, IIIB gp160-expressing vaccinia
- RGPGRAFVTI represents the active minimal epitope within the previously described immunodominant epitope P18IIIB (RIQRGP-GRAFVTIGK, gp160(308-322)
- External processing of P18IIIB results in the removal of the 2 C-terminal residues (GK) of I-10 by ACE (angiotensin-1-converting-enzyme) in sera to produce I-10, and this processing is essential for target cell presentation of RIQRGPGRAFVTIGK

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gp160(311–320)	gp160( )	RGPGRAFVTI	Vaccine	murine(H-2^d)	[Gherardi (2000)]

Vaccine: *Vector/type:* DNA, vaccinia *HIV component:* env *Stimulatory Agents:* IL-12

- Epitope name: P18. Induction of HIV-1 specific CD8 γ IFN secreting cells was enhanced when IL-12 and Env were given together in a prime, followed by a VV expressing Env boost
- If IL-12 was also delivered as a boost from the viral vector, impairment of the IL-12 effects was noted, indicating that the vaccination schedule can be a critical parameter for success with DNA and vaccinia vectors used in combination with immunomodulators
- The negative effect observed when IL-12 was delivered with the boost involved nitric oxide

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gp160(311–320)	Env( )	RGPGRAFVTI	Vaccine	murine(H-2^d)	[Xin (1999)]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* gp160, rev *Stimulatory Agents:* IL-15 and IL-2, IL-12

- Epitope name: P18. A study of the DNA vaccine pCMV160IIIB/REV with IL-15 and IL-2 or IL-12 expression plasmids.
- Intranasal immunization of BALB/c mice with HIV DNA and IL-15 plasmid induced increased Th1 and CTL responses
- Co-administration of IL-15 with IL-12 or IL-2 plasmids did not alter the effect of IL-15
- Both the CTL (peptide pulsed targets) and DTH response (injection of peptide into footpad) to this peptide was monitored
- The Ab response to NNTRKSIRIQRGPGRAFVTIGKIGN was monitored, and IL-15 co-administration resulted in a decrease in the IgG1/IgG2a ratio

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gp160(311–320)	Env( )	RGPGRAFVTI	Vaccine	murine(H-2^d)	[Villacres & Bergmann(1999)]

Vaccine: *Vector/type:* vaccinia, Sindbis *HIV component:* V3

- Epitope name: P18. HIV-1 epitope p18 was expressed in two different vaccine vectors and the CTL response was compared in BALB/c mice
- Class I tetramer staining showed that up to 13% of the CD8+ splenocytes were p18 specific in the acute response using vaccinia, only 4% using Sindbis
- vp18 had more γ IFN secreting splenocytes and activated CD4+ and CD8+ T-cells
- The overall decline in CD8+ T-cells in the transition into memory was 2-3 fold for both vectors
- Sindbis virus recombinants induced protective memory cytotoxic T-cells, although reduced quantitatively, without vaccinia associated inflamation and replication

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gp160(311–320)	gp160(318–327 IIIB)	RGPGRAFVTI	*in vitro* stimulation	murine(H-2^d)	[Takahashi (2001)]

- Epitope name: I-10. Pre-incubation of HIV-1 (IIIB) gp160 specific CTL with peptide without APCs reduced cytolytic activity 3.5 fold and induced peptide concentration dependent IL-2 unresponsiveness that might be due to IL-2Rβ down regulation
- An enhanced cytolytic activity was observed by addition of anti-IFN-γ, TNF-α or MIP-1β to I-10 suppressed CTLs

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gp160(311–320)	gp160( )	RGPGRAFVTI	Vaccine	murine(H-2^d)	[Shirai (2001)]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- Epitope name: P18. *Helicobacter pylori* induces Th1 responses early, but predominantly Th2 responses later in infection (at 6 weeks) – differentiation of HIV-1 gp160 CD4+ help and CD8+ CTL effector cells in response to HIV gp160-vaccinia vaccination is impaired in BALB/c mice infected with H. pylori

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gp160(311–320)	gp160(318–327 IIIB)	RGPGRAFVTI	Vaccine	murine(L^d)	[Tobery & Siliciano(1997)]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* env, nef

- Epitope name: P18. An HIV-1 Env vaccine was targeted for rapid cytoplasmic degradation
- The rapidly degraded form rapidly stimulated CTL to this peptide, faster than the normal vaccinia-env
- The rapidly degraded form also stimulated greater specific CTL lysis and higher CTLp frequencies than normal Env
- Similar results were obtained for a Nef protein designed for rapid degradation

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gp160(314–322)	gp120(314–322)	GRAFVTIGK	Peptide-HLA interaction	human(B27)	[Jardetzky (1991)]

- Study of peptide binding to HLA-B27

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gp160(337–361)	gp120(337–368 LAI)	KWNNTLKQIDSKLRE-QFGNNKTIIF	Vaccine	human(CD4+ CTL)	[Johnson (1994a)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- CD4+ CTL clones were obtained from an HIV-1 vaccinia-env vaccinee

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gp160(339–354)	gp120(339–361 LAI)	NNTLKQIDSKLREQFG	Vaccine	human(CD4+ CTL)	[Johnson (1994b)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- CD4+ CTL isolated from LAI IIIB gp160 vaccinees

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gp160(340–348)	gp120(346–354 CM243 CRF01)	RVLKQVTEK	HIV-1 infection	human(A11)	[Sriwanthana (2001)]

- Epitope name: E340-348. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was weakly reactive in HIV+ control study subject 053 who carried HLA-A11

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gp160(340–348)	gp120(346–354 CM243 CRF01)	RVLKQVTEK	HIV-1 infection	human(A11)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it
- This epitope was not conserved in other subtypes, and exact matches were rare

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gp160(340–349)	gp120( )	NTLKQIVIKL	Vaccine	chimpanzee(Patr-B*14)	[Balla-Jhagjhoorsingh (1999a)]

Vaccine: *Vector/type:* recombinant protein *Strain:* W6.ID *HIV component:* gp120

- An HIV-1 rgp120 vaccine induced strong humoral and cellular immune response in sibling chimpanzees, but only one of the two made a detectable CTL response to this Patr-B*14 restricted immunodominant epitope

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gp160(369–375)	gp120(374–380 BRU)	PEIVTHS	HIV-1 infection	human(A2)	[Dadaglio (1991)]

- Defined through blocking CTL activity, and Env deletions

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gp160(375–383)	gp120(379–387 LAI)	SFNCGGEFF	HIV-1 infection	human(B*1516)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*1516 epitope

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gp160(375–383)	gp120(375–383 IIIB)	SFTCGGEFF	HIV-1 infection	human(B15)	[Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- An additional variant that gave a positive, though reduced, CTL response: SSTCGGEFF and SFTCGGGFF
- SFTCGGGVF was an escape mutant

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gp160(375–383)	gp120(375–383 SF2)	SFNCGGEFF	HIV-1 infection	human(B15)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B15+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 1/1 group 2, and 0/1 group 3

gp160(375–383)	gp120(375–383 IIIB)	SFNCGGEFF	HIV-1 infection	human(B63,B15)	[Wilson (1997)]

- This is the optimal peptide for two CTL clones that recognize this epitope in the context of two different HLA molecules, Cw4 and B15
- Predominant form in proviral DNA of the individual with B15 restricted CTL was SFTCGGEFF and this was recognized
- Recognition of a minor autologous variant (SFNCRGEFF) from the B15 donor was greatly reduced

gp160(375–383)	gp120(376–383 PV22)	SFNCGGEFF	HIV-1 infection	human(C*0401)	[Brander & Goulder(2001)]

- C. Brander notes this is a C*0401 epitope

gp160(375–383)	gp120(376–383 PV22)	SFNCGGEFF	HIV-1 infection	human(Cw4)	[Johnson (1993)]

- Conserved epitope

gp160(375–383)	gp120(376–383 PV22)	SFNCGGEFF	HIV-1 infection	human(Cw4)	[Wolinsky (1996)]

- Longitudinal study of epitope variation *in vivo*

gp160(375–383)	gp120(376–383)	SFNCGGEFF	HIV-1 exposed seronegative, HIV-1 infection	human(Cw4)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-Cw4 women, 1/2 HEPS and 10/11 HIV-1-infected women recognized this epitope
- The dominant response to this HLA allele was to this epitope in 6 of the 10/11 responsive HIV-1-infected women, and not in the HEPS case

gp160(376–383)	gp120( )	FNCGGEFF		human(Cw4)	[Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive,
- HIV-2 sequence: TNCRGEFL – no cross-reactivity [Johnson (1993)]

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gp160(376–384)	gp120(376–384 IIIB)	FNCGGEFFY	HIV-1 infection	human(A29)	[Wilson (1997)]

- This is the optimal peptide for two CTL clones derived from two different donors
- FNCRGEFFY and FNCRGGFFY are major and minor autologous variants in one of the donors, and showed reduced or no stimulatory activity for CTL from the host
- The IIIB form and the form FNCAGEFFY were present in the other donor, and the CTL line had reduced activity with the FNCAGEFFY form relative to the index peptide

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gp160(376–384)	gp120(376–384 IIIB)	PNCGGEFFY	HIV-1 infection	human(A29)	[Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- PNCRGEFFY was an escape variant

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gp160(376–384)	gp120(376–384 LAI)	FNCGGEFFY	HIV-1 infection	human(A29)	[Mollet (2000)]

- Epitope name: E2. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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gp160(376–384)	gp120(376–384)	FNCGGEFFY	HIV-1 infection	human(B8)	[Oxenius (2000)]

- Epitope name: FNC. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- One of the 7/8 study subjects that were HLA B8 recognized this CTL epitope
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197

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gp160(376–387)	gp120(381–392 BRU)	KNCGGEFFYCNS	HIV-1 infection	human(A2)	[Dadaglio (1991)]

- Defined through blocking CTL activity, and Env deletions

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gp160(377–387)	gp120(377–387)	NSGGEFFYSNS		human(A2)	[Hickling (1990)]
• Peptides recognized by class I restricted CTL can bind to class II					
gp160(383–391)	gp120(385–393)	FYCNTTQLF	HIV-1 infection	human(A*2402)	[Ikeda-Moore (1997)]
• Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402					
• This peptide induced CTL in 1/4 HIV-1+ people tested					
• FYCNTTQLF bound to A*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained					
gp160(410–429)	gp120(410–429 PV22)	GSDTITLPCRIKQFINM-WQE	*in vitro* stimulation	human(CD4+DRA)	[Bouhdoud (2000)]
• CTL were studied through PBMC stimulation *in vitro* by gp120 pulsed autologous monocytes.					
• Human CD4+ CTL clone (Een217) is an MHC class II HLA-DRA restricted CTL clone that can lyse antigen presenting HLA-DRA-transfected murine L cells – natural variants of the epitope resulted in an anergic response					
• Low concentrations of the HXB2-derived variant (GSDTITLPCRIKQIINMWQK) induced T-cell anergy – higher concentrations could induce proliferation and cytotoxic activity					
• CDC42 (TGDIITLPCRIKQII-NRWQV), Eli (TNTNITLQCRIKQIIKMVAG) and Z3 (CTGNITLPCRIKQIIMNWQE) variants did not induce proliferation, cytotoxic or anergic responses					
gp160(416–424)	Env(413–421 SF2)	LPCRIKQII	HIV-1 infection	human(B*5101)	[Tomiyama (1999)]
• HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995)					
• 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%					
• Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed					
• Four of the six epitopes were highly conserved among B subtype sequences, LPCRIKQII is not conserved					
gp160(416–424)	gp160(416–424 LAI)	LPCRIKQII		human(B*5101)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*5101 epitope					
gp160(416–424)	gp120(378–385)	LPCRIKQII	HIV-1 exposed seronegative, HIV-1 infection	human(B51)	[Kaul (2001a)]
• ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers					
gp160(416–429)	gp120(410–429 H3DCG)	LPCRIKQFINMWQE	HIV-1 infection	human(DR4 CD4+)	[Siliciano (1988)]
• CD4+ CTL restricted by class II HLA-DR4, targets primed by CD4 mediated uptake of gp120					

gp160(416–435)	gp120(421–440 LAI)	LPCRIKQFINMWQEV-GKAMY	HIV-1 infection	human(A2)	[Dadaglio (1991)]
• Defined through blocking CTL activity, and Env deletions					
gp160(419–427)	gp120(419–427 HXB2)	RIKQIINMW		human(A*3201)	[Harrer (1996b), Brander & Goulder(2001)]
• C. Brander notes this is an A*3201 epitope					
gp160(419–427)	gp120(419–427)	RIKQIINMW?	HIV-1 infection	human(A29, A32)	[Betts (2000)]
• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant • Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes • 1/11 of the A2+ individuals was A29 and responded to RIKQIINMW, and another responder was A32 and these are thought to be presenting molecules • The sequence is unclear – Betts calls both peptide 30 and peptide 32 gp120 419–427 and the peptide sequences are not provided					
gp160(419–427)	gp120(424–432 LAI)	RIKQFINMW	HIV-1 infection	human(A32)	[Ray (1998)]
• Autologous virus was used to detect CTL in two individuals, and in both cases strain-specific autologous CTL were found • The autologous epitope sequence was RIKQIINMW, MN and RF were KIKQFINMW and RIKQFVNMW respectively, and all were reactive with CTL clones					
gp160(419–427)	gp120(420–428)	RIKQIINMW	HIV-1 infection	human(A32)	[Ferris (1999)]
• This epitope is processed by a TAP1/2 dependent mechanism					
gp160(421–435)	gp120(421–440 LAI)	KQFINMWQEVGKAMY	HIV-1 infection	human(A2)	[Dadaglio (1991)]
• Defined through blocking CTL activity, and Env deletions					
gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMY-A	HIV-1 exposed seronegative	human( )	[Pinto (1995)]
• CTL and T helper cell reactivity in healthcare workers exposed to HIV					
gp160(421–436)	gp120( )	KQIINMWQEVGKAMY-A	HIV-1 infection	chimpanzee( )	[Lubeck (1997)]
• Epitope-specific CTL detected in chimpanzees immunized with adenovirus-HIV-1 MN gp160 recombinant • CTL response may account for protection against subsequent HIV-1 SF2 challenge in a chimpanzee lacking neutralizing antibodies • Helper and cytotoxic T-cells can be stimulated by this peptide (T1)					
gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMY-A	HIV-1 infection	human(A2)	[Clerici (1991)]
• Helper and cytotoxic T-cells can be stimulated by this peptide (T1)					

gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMY-A	HIV-1 infection	human(A2)	[Cease (1987)]

- Helper and cytotoxic T-cells can be stimulated by this peptide (T1)

gp160(421–436)	gp120(428–443 IIIB)	KQIINMWQEVGKAMY-A	Vaccine	murine(H-$2^{a,b,f}$)	[Shirai (1992)]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- In a murine system multiple class I molecules can present to CTL

gp160(432–451)	gp120(439–458 IIIB)	KAMYAPPISGQIRCSS-NITG	Vaccine	Rhesus macaque( )	[Wagner (1998b)]

Vaccine: *Vector/type:* virus-like particle *HIV component:* gag, gp120, V3, CD4BS

- A VLP is a non-infectious virus-like particle self-assembled from HIV Pr55 gag – macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains Gag and Env specific CTL were stimulated in each case, and Ab response to gag and gp120 was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4 – despite the CTL and Ab response, immunized macaques were infected by intervenous challenge with SHIV chimeric challenge stock
- CTL specific for this epitope could be found both before and after SHIV challenge

gp160(434–443)	gp120(431–440)	MYAPPIGGQI	Vaccine	murine(H-$2K^d$)	[Duarte (1996)]

Vaccine: *Vector/type:* peptide

- Tolerization of CTL response with continued administration of soluble peptide

gp160(435–443)	Env( )	YAPPISGQI	Vaccine	Rhesus macaque( )	[Barouch (2000), Shen & Siliciano(2000)]

Vaccine: *Vector/type:* DNA *Strain:* 89.6 *HIV component:* SIVmac239 Gag and HIV-1 89.6P Env *Stimulatory Agents:* IL-2/Ig

- Epitope name: p41A. Monkeys that received the DNA vaccines augmented with IL-2/Ig were infected when challenged with pathogenic SHIV-89.6P, but had potent CTL responses, stable CD4+ T-cell counts, preserved virus-specific CD4+ T-cell responses, low to undetectable viral loads, and no evidence of disease or mortality by day 140 after challenge – monkeys that got a sham vaccine had high viral load, progressed to disease, and were half were dead by day 140
- IL-2/Ig consisting of interleukin-2 (IL-2) for immune stimulation, and the Fc portion of immunoglobulin G (IgG) for stability, was delivered either as protein or as DNA – both enhance the CTL response to vaccination, DNA IL-2/Ig giving the most intense response
- Responses to a dominant Mamu A*01 gag epitope SIV Gag p11C (CTPYDINQM) and a subdominant epitope HIV-1 Env p41A (YAPPISGQI) were tracked and had good durability prior to challenge, and the higher the prechallenge peak p11C CTL response, the lower the post-challenge viral load
- No NAb responses were detected in the vaccinated monkeys prior to challenge, and comparable peak NAb titers developed in vaccinated monkeys and control monkeys with preserved CD4+ T-cells
- Shen *et al*. 2000 is an accompanying commentary

gp160(435–443)	Env( )	YAPPISGQI	Vaccine	Rhesus macaque( )	[Barouch (2001b)]

Vaccine: *Vector/type:* vaccinia *Strain:* 89.6 *HIV component:* SIVmac239 Gag/Pol and HIV-1 89.6P Env *Stimulatory Agents:* IL-2/Ig

- Epitope name: p41A. Four monkeys were vaccinated with a modified vaccinia Ankara (MVA) vaccine that elicited strong CTL to the immunodominant SIV gag eptiope in 4/4 animals, and 1/4 made a response to the HIV Env epitope YAPPISGQI, as determined by tetramer staining and chromium release assays
- The animals were infected when challenged with pathogenic SHIV-89.6P, but had potent CTL responses, secondary NAb responses upon challenge, partial preservation of CD4+ T-cell counts, lower viral loads, and no evidence of disease or mortality by day 168 after challenge – monkeys that got a sham vaccine had high viral load, progressed to disease, and 2/4 were dead by day 168

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gp160(435–443)	( )	YAPPISGQI	SHIV infection	Rhesus macaque (Mamu A*01)	[Egan (1999)]

- SHIV-infected rhesus macaques have high frequencies of response to the SIVmac epitope gag p11C,C-M (CTPYDINQM) but only a fraction of A*01 monkeys tested have responses to SIVmac pol epitope STPPLVRLV and HIV-1 env epitope YAPPISGQI

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gp160(435–443)	gp41( )	YAPPISGQI	SHIV infection, Vaccine	Rhesus macaque (Mamu A*01)	[Barouch (2001a)]

Vaccine: *Vector/type:* vaccinia MVA, DNA *Strain:* 89.6, HXBc2 *HIV component:* SIV Gag and HIV-1 Env *Stimulatory Agents:* IL-2/Ig

- Epitope name: p41A. Mamu-A*01+ rhesus monkeys infected with SHIV-89.6 and SHIV-HXBc2 make immunodominant responses to SIV Gag p11C epitope (CTPYDINQM) and a subdominant response to HIV-1 Env p41A epitope (YAPPISGQI)
- The binding affinities are the same for the two epitopes to Mamu A*01, so that is not what dictates the dominance
- Monkeys vaccinated with MVA vectors carrying SIV gag/pol and HIV-1 env showed the same p11C epitope dominance and p41A epitope subdominance, but co-dominance was observed and the response to p41A increased when DNA vaccination was done using the SIV and HIV genes under CMV promotor control with IL-2-Ig adjuvant

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gp160(444–453)	Env( )	RCSSNITGLL		human(B56)	[De Groot (2001)]

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 of the predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay
- RCSSNITGLL was newly-defined as an epitope in this study, and was shown to stimulate an ELISPOT response, despite not detectably binding to HLA-B7

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gp160(489–508)	gp120(494–513 BRU)	VKIEPLGVAPTKAKRR-VVQR	HIV-1 infection	human(A2)	[Dadaglio (1991)]

- Defined through blocking CTL activity, and Env deletions

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gp160(519–543)	gp41(519–543)	FLGFLGAAGSTMGAA-SLTLTVQARC	HIV-1 infection	human(Cw7)	[Nehete (1998)]

- Three long-term non-progressors and one asymptomatic HIV+ individual were studied and found to have HLA class I C-restricted CD8+ Env-specific CTLs – Cw7 specific CTL were found against three peptides, including this one
- HLA-C antigens are expressed on lymphoid cells to a lesser extent, 10% of either HLA-A or HLA-B
- HLA-C confers protection against lysis by natural killer cells and by non-MHC-restricted effector T-cells and Cw7 directly governs this resistance to lysis – the authors hypothesize that pathogens that inhibit antigen expression and class I expression may particularly down regulate Cw7, thus triggering non-MHC restricted killing

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gp160(557–565)	gp41(557–565 IIIB)	RAIEAQQHL	HIV-1 infection	human( )	[Wilson (1996)]

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study
- RAIDAQQHL and RVIEAQQHL, naturally occurring variants, were found in the mother and are recognized

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gp160(557–565)	gp41(557–565)	RAIEAQQHL	HIV-1 infection	human( )	[Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- 1/11 of the A2+ individuals was HLA A*0201, A32, B60, B78, and responded to RAIEAQQHL, previously noted to be B51

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gp160(557–565)	gp41(557–565 IIIB)	RAIEAQQHL	HIV-1 infection	human(B*5101)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*5101 epitope

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gp160(557–565)	gp41(557–665)	RAIEAQQWQ	HIV-1 infection	human(B*5101)	[Samri (2000)]

- Epitope name: E3. The epitope was recognized by patient 246#1 in a study of the effects of therapy escape mutations on CTL recognition

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gp160(557–565)	gp41(557–565 IIIB)	RAIEAQQHL	HIV-1 infection	human(B15)	[Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- This epitope was invariant in both the mother and her infant

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gp160(557–565)	gp41(557–565 IIIB)	RAIEAQQHL	HIV-1 infection	human(B51)	[Sipsas (1997)]

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB
- KAIEAQQHL, a variant found in HIV-1 NY5CG, was also recognized
- RAIEAQQHM, a variant found in HIV-1 JRCSF, was also recognized
- RAIDAQQHL, a variant found in HIV-1 ETR, was also recognized
- RAIKAQQHL, a variant found in HIV-1 CDC42, was also recognized

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gp160(557–565)	gp41(557–565)	RAIEAQQHL	HIV-1 infection	human(B51)	[Ferris (1999)]

- This epitope can be processed by a TAP1/2 dependent mechanism

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gp160(557–565)	gp41(557–565)	RAIEAQQWQ	HIV-1 infection	human(B51)	[Oxenius (2000)]

- Epitope name: RAI. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- None of the 8 study subjects recognized this epitope but none were HLA B51+

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gp160(557–565)	gp41(47–55)	RAIEAQQHL	HIV-1 infection	human(B51)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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gp160(557–565)	gp41(557–565 LAI)	RAIEAQQHL	HIV-1 infection	human(B51)	[Mollet (2000)]

- Epitope name: E3. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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gp160(565–573)	Env(731–739)	LLQLTVWGI	HIV-1 infection	human(A2 supertype)	[Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype), while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind four of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)

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gp160(565–573)	Env(731–739)	KLVGKLNWA	HIV-1 infection	human(A2 supertype)	[Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype), while the effector cells of long-term non-progressors recognized far fewer epitopes
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- This epitope can bind four of the five HLA-A2 supertypes alleles (A*0201, A*020 2, A*0203, A*0206 and A*6802)
- Tetramer staining with A2, β2-microglobulin, and either SLYNTVATL, KLVGKLNWA, or LTFGWCFKL revealed that tetramers detected more HIV-specific cells in LTNP than in progressors, activated effector cells were the minority population, and ELISPOT correlated better with the effector cell subpopulation than the total tetramer stained population

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gp160(570–589)	gp41(571–590 LAI)	VWGIKQLQARILAVER-YLKD	Vaccine	human(CD4+ CTL(DR-1))	[Kent (1997a)]

Vaccine: *Vector/type:* vaccinia prime with rgp160 boost *Strain:* LAI *HIV component:* gp160

- VWGIKQLQARILAVERYLKD, present in HIV-1 LAI, was the immunizing strain
- VWGIKQLQARVLAVERYLKD, present in HIV-1 MN, was also recognized
- VWGIKQPQARVLAVERYLRD was the form carried by the autologous strain that infected the vaccinee
- Lysis of the target cells by CD4+ CTL was inhibited with the addition of the peptide representing the autologous strain
- The infecting virus epitope also antagonized the proliferative functions of the CD4+ CTL clone
- The behavior of the autologous strain presents a possible mechanism for vaccine failure since the infecting virus not only escapes CTL activity, but inhibits the ability of CTL to recognize other variants

gp160(572–590)	gp41(572–590 BRU)	GIKQLQARILAVERYL-KDQ	Vaccine	human(DPw4.2)	[Hammond (1991)]

Vaccine: *Vector/type:* recombinant protein *Strain:* BRU *HIV component:* gp160

- CD4+ CTL

gp160(575–599)	gp41(575–599 IIIB)	QLQARILAVERYLKDQ-QLLGIWGCS	HIV-1 infection	human(B14)	[Jassoy (1992)]

- Epitope recognized by CTL clone derived from CSF

gp160(583–592)	gp41(583–592 PV22)	VERYLKDQQL	HIV-1 infection	human(B14)	[Jassoy (1993)]

- HIV-1 specific CTLs release γ-IFN, and α- and β-TNF

gp160(584–592)	gp41(589–597 SF2)	ERYLKDQQL	HIV-1 infection	human(B14)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B14+ individuals that had a CTL response to this epitope broken down by group: 3/3 group 1, 1/2 group 2, and 0/0 group 3

gp160(584–592)	gp41(584–592)	ERYLKDQQL	HIV-1 infection	human( )	[Price (1995)]

- Study of cytokines released by HIV-1 specific activated CTL

gp160(584–592)	gp41(584–592)	ERYLKDQQL	HIV-1 infection	human( )	[Borrow (1994)]

- Three out of five patients with HIV-1 symptomatic infection controlled their viral infection well and mounted an early, strong HIV-1 specific MHC restricted CTL response
- One of the three, study subject BORI, specifically recognized this peptide

gp160(584–592)	gp41(584–592 HXB2)	ERYLKDQQL	HIV-1 infection	human(A32, B14)	[Mollet (2000)]

- Epitope name: E4. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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gp160(584–592)	gp41(584–592 PV22)	ERYLKDQQL	HIV-1 infection	human(B*1402)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*1402 epitope

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gp160(584–592)	gp41( )	ERYLKDQQL	HIV-1 infection	human(B14)	[Wagner (1998a)]

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1 α and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules

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gp160(584–592)	gp41(584–592)	ERYLKDQQL	HIV-1 infection	human(B14)	[Kalams (1999b)]

- Two patients were followed before and after HAART – reduced plasma HIV-1 RNA levels resulted in a decline in HIV *in vivo* activated specific CTL such that by day 260 CTL activities were undetectable
- ERYLKDQQL was the dominant response in one of the individuals, SLYNTVATL subdominant
- Sporadic breakthrough in viremia resulted in increases in CTLp
- Peptide-tetramer staining demonstrated that declining levels of *in vivo*-activated CTL were associated with a decrease in expression of CD38
- Memory CTL frequency directed against Vac-Gag, Vac-RT, Vac-Env, and Vac-Nef initially increased with HAART and then decreased with the decline of the viral load

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gp160(584–592)	gp41(591–599 SF2)	ERYLKDQQL	HIV-1 infection	human(B14)	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160
- One of these 11 had CTL response to this peptide
- The responding subject was HLA-A3, -A32, -B7, -B14

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gp160(584–592)	gp41(591–599 SF2)	ERYLKDQQL	HIV-1 infection	human(B14)	[Cao (1997)]

- The consensus sequence for clades B, C, and D is ERYLKDQQL
- The consensus sequence for clade A is ERYLRDQQL and it is equally reactive
- The consensus sequence for clade E is ERYLKDQKF and it is not reactive

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gp160(584–592)	gp41( )	ERYLKDQQL	HIV-1 exposed seronegative	human(B14)	[Rowland-Jones (1998a)]

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating
- The A and D subtype consensus are identical to the B clade epitope, ERyLkDQQL

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gp160(584–592)	gp41(584–592)	ERYLKDQQL	HIV-1 infection	human(B14)	[Sipsas (1997)]

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB

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gp160(584–592)	gp41(584–592)	ERYLKDQQL	HIV-1 infection	human(B14)	[Yang (1996)]

- CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones
- The distinction was thought to be due to lower expression of RT relative to Env and Gag
- CTL can lyse infected cells early after infection, possibly prior to viral production

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gp160(584–592)	gp41(584–592)	ERYLKDQQL	HIV-1 infection	human(B14)	[Yang (1997a)]

- CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*
- CTL produced HIV-1-suppressive soluble factors – MIP-1α, MIP-1β, RANTES, after antigen-specific activation
- CTL suppress HIV replication more efficiently in HLA-matched cells

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gp160(584–592)	gp41(584–592 PV22)	ERYLKDQQL	HIV-1 infection	human(B14)	[Johnson (1992)]

- Two overlapping CTL epitopes were mapped with different HLA restriction (also see YLKDQQLL HLA-B8)

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gp160(584–592)	gp41(584–592 PV22)	ERYLKDQQL	HIV-1 infection	human(B14)	[Jassoy (1993)]

- HIV-1 specific CTLs release γ-IFN, and α- and β-TNF

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gp160(584–592)	gp41(584–592 HXB2)	ERYLKDQQL	HIV-1 infection	human(B14)	[Kalams (1994), Kalams (1996)]

- Longitudinal study of T-cell receptor usage in a single individual
- Persistence of oligoclonal response to this epitope for over 5 years

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gp160(584–592)	gp41(584–592)	ERYLKDQQL	Peptide-HLA interaction	human(B14)	[DiBrino (1994a)]

- Epitope studied in the context of HLA-B14 binding

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gp160(584–592)	gp41(584–592)	ERYLKDQQL	HIV-1 infection	human(B14)	[Hammond (1995)]

- This peptide can be processed for HLA-B14 presentation in a TAP-1/2 independent pathway

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gp160(584–592)	gp41(584–592)	ERYLKDQQL	HIV-1 infection	human(B14)	[Kalams (1996)]

- CTL response to this epitope was studied in 5 HLA-B14 positive persons
- CTL responses were detected in all five, and CTL clones were isolated from 4/5

- A diverse repertoire of TCRs recognized this epitope, with similar fine specificities
- 3/5 subjects showed no variation in viral sequence, 2/5 had a dominant variant that resulted in poor recognition, ERYLQDQQL
- A minor CTL response specific for the ERYLQDQQL could be detected by two individuals, but the major CTL response was to the ERYLKDQQL form even when it was the minority form
- Some single amino acid substitutions were well tolerated by most of the CTL clones tested, but others, particularly in the center three amino acid positions, abrogated peptide stimulatory activity

gp160(584–592)	gp120(584–592)	ERYLKDQQL	HIV-1 infection	human(B14)	[Ferris (1999), Hammond (1995)]

- This epitope is processed by both TAP1/2 dependent and independent mechanisms

gp160(584–592)	gp41( )	ERYLKDQQL		human(B14)	[Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective
- HIV-2 sequence: EKYLQDQAR – no cross-reactivity [Johnson (1992)]

gp160(584–592)	gp41( )	ERYLKDQQL	HIV-1 infection	human(B14)	[Goulder (2001b)]

- Epitope name: EL9. Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation
- Recognized by two A*0201-positive chronically infected subjects

gp160(584–592)	gp41(584–592)	ERYLKDQQL	HIV-1 infection	human(B14)	[Islam (2001)]

- Epitope name: 588K. Transcript frequencies of four CTL clones from patient 115, with a chronic and stable HIV-1 infection, were tracked in a longitudinal study of samples collected 6-11 years post infection: clones M21 and E15 recognize ERYLKDQQL, clone D87 recognizes variant ERYLQDQQL, and clone p175b recognizes the A2 epitope SLYNTVATL
- CTL clone M21 uses the Vβ 4, CDR3 VKDGA, Jβ 1.2 TCR β gene, and clone E15 uses the Vβ 4, CDR3 VEDWGGAS Jβ 2.1 TCR β gene, and D87 uses Vβ8, ALNRVD, Jβ2.1
- Responses were stable even through HAART with undetectable viral loads but frequencies varied over time by 100-fold, ranging from 0.012% of the total population for SLYNTVATL at its lowest point to 3.78% for M21, with the relative frequencies of clones shifting over time

gp160(584–592)	gp41(589–597)	ERYLRDQQL	HIV-1 exposed seronegative, HIV-1 infection	human(B14)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

gp160(584–592)	gp41( )	ERYLKDQQL	HIV-1 infection	human(B14)	[Severino (2000)]

- Primary HLA-B14+ CD4+ CD3+ and HLA-mismatched lymphocytes from uninfected donors were infected with JRCSF after isolation then cocultured with the B14-restricted CTL clone 15160/D75 specific for ERYLKDQQL, and viral inhibition was MHC-restricted
- Primary monocytes and monocyte-derived DC were generated from the same donors, replication of HIV-1 in these cell types was less efficient than in lymphocytes and could also be inhibited by MHC-restricted CTL
- DC-lymphocyte cluster cultures allowed vigorous viral replication and MHC-restricted CTL viral inhibition was blunted or lost depending on the ratio of DC to CD4+ lymphocyte in the culture

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gp160(584–592) gp41( ) ERYLKQQL HIV-1 infection human(B14) [Altfeld (2000)]

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual

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gp160(584–592) gp41( ) ERYLKDQQL HIV-1 exposed seronegative human(B14, B*1402) [Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among B and D clade viruses
- The clade A version of the epitope is ERYLRDQQL

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gp160(585–592) gp41(584–591 SF2) RYLRDQQL HIV-1 infection human(A*2402) [Ikeda-Moore (1997)]

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402
- This peptide induced CTL in 2/4 HIV-1+ people tested
- RYLRDQQL bound to A*2402 weakly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained

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gp160(585–592) gp41(590–597 LAI) RYLKDQQL HIV-1 infection human(B27) [Shankar (1996)]

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gp160(585–593) gp41(584–591 SF2) RYLRDQQLL HIV-1 infection human(A*2402) [Ikeda-Moore (1997)]

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402
- This peptide induced CTL in 4/4 HIV-1+ people tested
- RYLRDQQLL bound to A*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained

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gp160(585–593) gp41(591–598 LAI) RYLKDQQLL human(A*2402) [Brander & Goulder(2001)]

- C. Brander notes this is an A*2402 epitope

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gp160(585–595) gp41(584–591 SF2) RYLRDQQLLGI HIV-1 infection human(A*2402) [Ikeda-Moore (1997)]

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402

- This peptide induced CTL in 4/4 HIV-1+ people tested
- RYLRDQQLLGI bound to A*2402 with medium strength, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained

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gp160(586–593) gp160( ) YLRDQQLL HIV-1 infection human( ) [Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized in 1/22 HEPS sex worker controls, ML887

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gp160(586–593) gp41(584–591 NL43) YLKDQQLL HIV-1 infection human(A*2402) [Dai (1992)]

- The lysine (K) is critical for eliciting a HLA-A24 CTL response
- C. Brander notes that this is an A*2402 epitope in the 1999 database, and suggested that the epitope is RYLKQQLL

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gp160(586–593) gp41(591–598) YLRDQQLL HIV-1 exposed seronegative, HIV-1 infection human(A24) [Kaul (2001a)]

- Variants (R)YL(R/K)DQQLL are specific for the A/B clade
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-A24 women, 3/4 HEPS and 10/10 HIV-1-infected women recognized this epitope, and (R)YL(R/K)DQQLL tended to be reactive in HEPS and infected women, RDYVDRFFKTL in infected women only
- The dominant response to this HLA allele was to this epitope in all 3/4 HEPS cases but in only 4 of the 10/10 HIV-1-infected women
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort

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gp160(586–593) gp41(580–587 CM243 CRF01) YLKDQQLL HIV-1 infection human(A24) [Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested
- The only HLA-A24 FSW tested did not recognized the E clade version of this epitope RYLKDQKLL, which differs from the previously defined B clade version by one amino acid, YLKDQQLL, with an additional amino acid added on

- This epitope was only conserved in CRF01 (subtype E), and identities were rare

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gp160(586–593) gp41(586–593 LAI) YLKDQQLL HIV-1 infection human(A24,B8) [Mollet (2000)]

- Epitope name: E1. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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gp160(586–593) gp41(586–593) YLKDQQLL HIV-1 infection human(B*0801) [Brander & Goulder(2001)]

- C. Brander notes this is a B*0801 epitope

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gp160(586–593) gp41(586–593) YLKDQQLL HIV-1 infection human(B8) [Johnson (1992)]

- Two overlapping CTL epitopes were mapped with different HLA restriction (also see ERYLKDQQL HLA-B14)

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gp160(586–593) gp41(586–593) YLKDQQLL Peptide-HLA interaction human(B8) [Sutton (1993)]

- Predicted epitope based on B8-binding motifs, from larger peptide QLQARILAVERYLKDQQLLGIWGCS

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gp160(586–593) gp41(76–83) YLKDQQLL human(B8) [Goulder (1997g)]

- Included in a study of the B8 binding motif

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gp160(586–593) gp41( ) YLKDQQLL human(B8) [Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive
- HIV-2 sequence: YLQDQARL – no cross-reactivity [Johnson (1992)]

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gp160(586–593) gp41(586–593) YLKDQQLL HIV-1 exposed seronegative, HIV-1 infection human(B8) [Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

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gp160(586–593) gp41(586–593) YLKDQQLL HIV-1 infection human(B8) [Day (2001)]

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual

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gp160(586–598) gp41(586–598) YLRDQQLLGIWGC HIV-1 infection human(Cw7) [Nehete (1998)]

- Three long-term non-progressors and one asymptomatic HIV+ individual were studied and found to have HLA class I C-restricted CD8+ Env-specific CTLs – Cw7 specific CTL were found against three peptides, including this one
- HLA-C antigens are expressed on lymphoid cells to a lesser extent, 10% of either HLA-A or HLA-B

- HLA-C confers protection against lysis by natural killer cells and by non-MHC-restricted effector T-cells and Cw7 directly governs this resistance to lysis – the authors hypothesize that pathogens that inhibit antigen expression and class I expression may particularly down regulate Cw7, thus triggering non-MHC restricted killing

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gp160(594–608) gp41( ) GIWGCSGKLICTTAV HIV-1 infection human(B57) [Jin (1998b)]

- Progressive HIV-1 infection and CD4 decline was associated decreased the IL-2-expandable HIV-1 CTL response in 10 asymptomatic HIV-infected patients – this observation may be partially due to a reduction and impaired function of T helper cells, CTL exhaustion and APC dysfunction
- Continued presence of HIV-1 specific memory cells (CTLp) was observed in three patients, one to GIWGCSGKLICTTAV, one to ALIWEDLRSLCLFSY, and one to PIPIHYCAPAGFAILKCNNK

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gp160(606–614) gp41(605–615 LAI) TAVPWNASW Vaccine human(B*3501) [Brander & Goulder(2001)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- C. Brander notes this is a B*3501 epitope

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gp160(606–614) gp41(606–614 HXB2) TAVPWNASW HIV-1 infection human(B*3501) [Ferris (1996)]

- Natural form of this peptide is not glycosylated, suggesting initial Class I processing may occur in the cytosol

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gp160(606–614) gp41(605–615 LAI) TAVPWNASW Vaccine human(B35) [Johnson (1994b)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- Epitope for vaccine induced CD8+ clone

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gp160(606–614) gp41(606–614 LAI) TAVPWNASW Vaccine human(B35) [Johnson (1994a)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- HLA restricted CTL response to epitope in HIV-1 vaccinia-env vaccinees

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gp160(606–614) gp41(606–614 LAI) TAVPWNASW Vaccine human(B35) [Hammond (1995)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- Peptide only processed by a TAP-1/2-dependent pathway

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gp160(606–614) gp41(606–614) TAVPWNASW HIV-1 infection human(B35) [Ferris (1999)]

- This epitope is processed by a TAP1/2 dependent mechanism

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gp160(606–614) gp41( ) TAVPWNASW HIV-1 exposed seronegative human(B35) [Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among A, B and D clade viruses

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gp160(606–614)	gp41(606–614)	TAVPWNASW	HIV-1 exposed seronegative, HIV-1 infection	human(B35)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

gp160(634–648)	gp41(641–655 SF2)	EIDNYTNTIYTLLEE	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160
- One of these 11 had CTL response to this peptide
- The responding subject was HLA-A1, A2, B51, and B57

gp160(678–686)	Env(679–687 clade B)	WLWYIKIFI	Vaccine	human(A2.1)	[Kundu (1998a)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- Ten HIV-1+ HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses

gp160(680–689)	gp41(679–687 SF2)	WYIKIFIFMI	HIV-1 infection	human(A*2402)	[Ikeda-Moore (1997)]

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402
- This peptide induced CTL in 1/4 HIV-1+ people tested
- WYIKIFIFMI bound to A*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained

gp160(685–693)	Env(686–694 clade B)	FIMIVGGLV	Vaccine	human(A2.1)	[Kundu (1998a)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- Ten HIV-1+ HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses

gp160(700–708)	gp41(705–714)	AVLSVVNRV	HIV-1 infection	human(A2)	[Ferris (1999)]
• This epitope is processed by a TAP1/2 dependent mechanism					
gp160(701–720)	gp41(701–720 BH10)	VLSIVNRVRQGYSPLS-FQTH	HIV-1 infection	human(A32)	[Safrit (1994a)]
• Recognized by CTL derived from acute seroconverter					
gp160(704–712)	gp160(704–712 LAI)	IVNRNRQGY		human(A*3002)	[Brander & Goulder(2001), Goulder (2001b)]
• C. Brander notes this is an A*3002 epitope					
gp160(704–712)	gp41( )	IVNRVRQGY	HIV-1 infection	human(A*3002)	[Goulder (2001a)]
• Epitope name: IY9 (gp41). HLA-A*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule • A rapid method was developed combining ELISPOT with intracellular IFN-γ staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood • Two individuals were studied: Subject 199 (HLA A*0201/*3002 B*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A*3002/ B53/*5801 Cw4/7) an African-Caribbean • In both HLA-A*3002 individuals the response to RSLYNTVATLY was dominant • In subject 199 four additional A*3002 epitopes were identified • Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)					
gp160(747–755)	gp41(747–755)	RLVNGSLAL	HIV-1 infection	human(A2)	[Parker (1992)]
• Studied in the context of HLA-A2 peptide binding					
gp160(747–755)	gp41(741–749 CM243 CRF01)	RLVSGFLAL	HIV-1 infection	human(A2)	[Sriwanthana (2001)]
• Epitope name: E747-755. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand • HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed • This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2					
gp160(747–755)	gp41(741–749 CM243 CRF01)	RLVSGFLAL	HIV-1 infection	human(A2)	[Bond (2001)]
• HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested					

- 2/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by two amino acids, RLVNGSLAL
- This epitope was somewhat conserved 4/8 subtypes: CRF01 (E), B, C, and G

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gp160(754–768) gp41( ) ALIWEDLRSLCLFSY HIV-1 infection human(B55) [Jin (1998b)]

- Progressive HIV-1 infection and CD4 decline was associated decreased the IL-2-expandable HIV-1 CTL response in 10 asymptomatic HIV-infected patients – this observation may be partially due to a reduction and impaired function of T helper cells, CTL exhaustion and APC dysfunction
- Continued presence of HIV-1 specific memory cells (CTLp) was observed in three patients, one to GIWGCSGKLICTTAV, one to ALIWEDLRSLCLFSY, and one to PIPIHYCAPAGFAILKCNNK

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gp160(767–775) gp41(766–774 SF2) SYRRLRDLL HIV-1 infection human(A*2402) [Ikeda-Moore (1997)]

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402
- This peptide induced CTL in 1/4 HIV-1+ people tested
- SYRRLRDLL bound to A*2402 moderately, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained

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gp160(767–780) gp41(606–614 LAI) SYHRLRDLLLIVTR HIV-1 infection human(A31) [Hammond (1995)]

- Peptide only processed by a TAP-1/2-dependent pathway
- CTL from an acute seroconverter

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gp160(769–777) gp41(769–777 BH10) HRLRDLLLI HIV-1 infection human( ) [Safrit (1994a)]

- Recognized by CTL derived from acute seroconverter

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gp160(770–778) Env(679–777) RLRDLLLIV HIV-1 infection human(A*0201) [Kmieciak (1998a)]

- Epitope name: 5.3. CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL – all have A2 anchor residues
- The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*
- Peptides 5.3 and D2 bound to HLA A*0201 with low affinity and were variable, particularly D2;

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gp160(770–780) gp41(775–785) RLRDLLLIVTR HIV-1 infection human( ) [Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- 1/11 of the HLA A2+ was HLA A*0201, A31, B8, B51 and responded to this epitope that has been previously noted to be HLA A3.1, as well as seven others

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gp160(770–780) gp41(768–778 NL43) RLRDLLLIVTR HIV-1 infection human(A*0301) [Takahashi (1991)]

- CD8+ T-cell clone

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gp160(770–780)	gp41(775–785 LAI)	RLRDLLLIVTR	HIV-1 infection	human(A*0301)	[Brander & Goulder(2001)]
• C. Brander notes this is an A*0301 epitope					
gp160(770–780)	gp41(770–780 BH10)	RLRDLLLIVTR	HIV-1 infection	human(A*3101)	[Safrit (1994a), Safrit (1994b)]
• Recognized by CTL derived from acute seroconverter • C. Brander notes that this is an A*3101 epitope in the 1999 database					
gp160(770–780)	gp160(770–780 LAI)	RLRDLLLIVTR		human(A*3101)	[Brander & Goulder(2001)]
• C. Brander notes this is an A*3002 epitope					
gp160(770–780)	gp41(768–778 NL43)	RLRDLLLIVTR	HIV-1 infection	human(A3)	[Cao (1997)]
• The consensus peptide of clade B is RLRDLLLIVTR • The consensus peptide of clades A, C and E is RLRDFILIVTR and it is less reactive • The consensus peptide of clade D is SLRDLLLIVTR and it is less reactive					
gp160(770–780)	gp41(775–785)	RLRDLLLIVTR	HIV-1 exposed seronegative, HIV-1 infection	human(A3)	[Kaul (2001a)]
• ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers					
gp160(770–780)	gp41(770–780)	RLRDLLLIVTR	HIV-1 infection	human(A3)	[Day (2001)]
• The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP) • Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person • All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant					
gp160(770–780)	gp41(770–780)	RLRDLLLIVTR	HIV-1 infection	human(A31)	[Ferris (1999), Hammond (1995)]
• This epitope is processed by a TAP1/2 dependent mechanism					
gp160(777–785)	gp41(782–790 LAI)	IVTRIVELL		human(A*6802)	[Brander & Goulder(2001)]
• C. Brander notes this is an A*6802 epitope					
gp160(781–802)	gp120(788–809)	IVELLGRRGWEALKY-WWNLLQY	*in vitro* stimulation	human( )	[Lieberman (1995)]
• HIV-specific CTL lines developed by *ex vivo* stimulation with peptide					

gp160(781–802)	gp41(788–809 HXB2)	IVELLGRRGWEALKY-WWNLLQY	HIV-1 infection	human(B27)	[Lieberman (1992)]
• CTL epitope defined by T-cell line and peptide mapping					
gp160(786–794)	gp41(791–799 LAI)	GRRGWEALK	HIV-1 infection	human(B27)	[McMichael & Walker(1994)]
• Review of HIV CTL epitopes • Also: J. Liebermann 1992 and pers. comm. J. Liebermann					
gp160(786–795)	gp41(791–800 LAI)	GRRGWEALKY	HIV-1 infection	human(B*2705)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*2705 epitope					
gp160(786–795)	gp41(791–800 LAI)	GRRGWEALKY	HIV-1 infection	human(B27)	[Lieberman(1998)]
• Optimal peptide mapped by titration J. Lieberman, Pers. Comm.					
gp160(786–795)	gp41(786–795)	GRRGWEALKY	HIV-1 infection	human(B27)	[Day (2001)]
gp160(794–802)	gp160(794–802 LAI)	KYCWNLLQY		human(A*3002)	[Brander & Goulder(2001), Goulder (2001b)]
• C. Brander notes this is an A*3002 epitope					
gp160(794–802)	gp41( )	KYCWNLLQY	HIV-1 infection	human(A*3002)	[Goulder (2001a)]
• Epitope name: KY9 (gp41). HLA-A*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule • A rapid method was developed combining ELISPOT with intracellular IFN-γ staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood • Two individuals were studied: Subject 199 (HLA A*0201/*3002 B*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A*3002/ B53/*5801 Cw4/7) an African-Caribbean • In both HLA-A*3002 individuals the response to RSLYNTVATLY was dominant • In subject 199 four additional A*3002 epitopes were identified • Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)					
gp160(794–814)	gp41( )	KYCWNLLQYWSQELK-NSAVSL	HIV-1 infection	human( )	[Altfeld (2000)]
• This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual • The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined					

gp160(795–816)	gp41(802–823 HXB2)	YWWNLLQYWSQELKN-SAVNLLN	HIV-1 infection	human( )	[Lieberman (1992)]

- CTL epitope defined by T-cell line and peptide mapping

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gp160(799–807)	Env(800–808 clade B)	LLQYWSQEL	Vaccine	human(A2.1)	[Kundu (1998a)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- Ten HIV-1+ HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses

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gp160(805–814)	gp41(810–819 LAI)	QELKNSAVSL		human(B*4001)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*4001,B60 epitope

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gp160(805–814)	gp41( )	QELKNSAVSL	HIV-1 infection	human(B60(B*4001)	[Altfeld (2000)]

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes
- B60 is present in 10-20% of the Caucasoid and very common in Asian populations

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gp160(805–814)	gp41(805–814)	QELKNSAVSL	HIV-1 infection	human(B60/B61)	[Day (2001)]

- No immunodominant responses were detected to five B61-restricted epitopes tested
- All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response

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gp160(813–822)	gp41(814–823 LAI)	SLLNATDIAV	Vaccine	human(A*0201)	[Dupuis (1995)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- Of two CTL clones, one reacted only with 815-823, the other with 814-823 and 815-823
- Noted to be A*0201 in Brander *et al*., 1999 database

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gp160(813–822)	gp41(818–827 LAI)	SLLNATDIAV	Vaccine	human(A*0201)	[Brander & Goulder(2001)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- C. Brander notes this is an A*0201 epitope

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gp160(813–822)	gp41(814–823)	SLLNATDIAV	HIV-1 infection	human(A2)	[Kundu (1998b)]

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients

- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated
- SLLNATDIAV is a conserved HLA-A2 epitope included in this study – 4/6 patients had this sequence as their HIV direct sequence, and 3 of these had a detectable CTL response – the other two had either the sequence SLFNAIDIAV or SLLNTTDIVV and no detectable CTL response
- CTL demonstrated against peptide-coated target, epitope is naturally processed and enhancible with vaccine

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gp160(813–822) gp41(818–827) SLLNATDIAV HIV-1 infection human(A2) [Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes, including this epitope

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gp160(813–822) gp41( ) SLLNATAIAV HIV-1 infection human(A2) [Goulder (2001b)]

- Epitope name: SV10. Dominant CTL epitope in acute infection of patient AC13– response to this epitope corresponded to reduction of initial viremia
- Several other subdominant CTL epitopes were identified in the acute phase, but a response to SL9, SLYNTVATL, was not evident until 18 months post-presentation

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gp160(813–822) gp41(77–85 SF2) SLLNATDIAV HIV-1 infection human(A2) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 2/6 group 2, and 1/4 group 3

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gp160(813–822) gp41(814–823 CM243 CRF01) SLLNATAIAV HIV-1 infection human(A2) [Sriwanthana (2001)]

- Epitope name: E813-82. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was reactive in HIV+ control study subjects 125 and 144 who carried HLA-A2

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gp160(813–822) gp41(814–823 CM243 CRF01) SLLNATAIAV HIV-1 infection human(A2) [Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested

- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by one amino acid, SLLNATDIAV
- This epitope was somewhat conserved 4/8 subtypes: CRF01 (E), B, D, and F

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gp160(813–822) gp41(813–822) SLLNATDIAV HIV-1 infection human(A2) [Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person

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gp160(813–822) Env(814–823 clade B) SLLNATDIAV Vaccine human(A2.1) [Kundu (1998a)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- Ten HIV-1+ HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses
- CTL to overlapping peptides in this region gave a positive response in the greatest number of patients
- ALTERNATIVE EPITOPES: LLNATDIAV and LLNATDIAVA – CTL were induced by vaccine in those that had the sequence SLLNATAIAVA in their own infection, but not in those with: NLLNTIAIAVA or NLFNTTAIAVA or SLLNATAITVA

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gp160(813–822) gp41( ) SLLNATDIAV HIV-1 infection human(A68) [Altfeld (2001d)]

- Epitope name: gp41 SV10. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- This epitope binds to three HLA-A2 supertype alleles: A*6802 (highest affinity), A*0202 and A*0203 (but not A*0201 and not A*0206)
- This epitope did not elicit an ELISPOT response in 22 chronic HIV HLA-A2 infections, but elicited a strong response in 1/12 acute HLA-A2 infections – this individual, AC13, was HLA A*0201/68 B44/14 and also had a strong response to HLA-A2 vpr epitope AIIRILQQL

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gp160(814–822) Env(815–823) LLNATAIAV HIV-1 infection human(A*0201) [Kmieciak (1998a)]

- Epitope name: D2. CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL – all have A2 anchor residues;
- The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*;
- Peptides 5.3 and D2 bound to HLA A*0201 with low affinity and were variable, particularly D2;
- Substitutions in peptide D2: `---TI----` did not abrogate the response, but diminished it;
- In a longitudinal study, the CTL response to the variable D2 epitope diminished over time, while the response to the conserved epitope D1 stayed higher;

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gp160(814–822) gp41(815–823 LAI) LLNATDIAV Vaccine human(A2) [Dupuis (1995)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- Of two CTL clones, one reacted only with 815-823, the other with 814-823 and 815-823

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gp160(814–822) Env(815–823) LLNATAIAV HIV-1 infection human(A2) [Kmieciak (1998b)]

- Increased CTL response to cells expressing a VV construct ΔV3 mutant compared with a full-length env gene product

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gp160(822–832) gp41( ) VAEGTDRVIEI HIV-1 infection human( ) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of individuals that had a CTL response to this epitope (HLA presenting molecule uncertain) broken down by group: 0 group 1, 1 group 2, and 0 group 3

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR HIV-1 exposed seronegative human( ) [Pinto (1995)]

- Epitope name: HP53. CTL and T helper cell reactivity in healthcare workers exposed to HIV

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR HIV-1 infection human(A2) [Clerici (1991)]

- Epitope name: HP53. Helper and cytotoxic T-cells can be stimulated by this peptide (Th4)

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR Vaccine murine(H-$2^{d,p,u,q}$) [Shirai (1992)]

Vaccine: *Vector/type:* vaccinia *Strain:* IIIB *HIV component:* gp160

- Epitope name: HP53. In a murine system multiple class I molecules can present to CTL

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gp160(827–841) gp41(834–848 IIIB) DRVIEVVQGAYRAIR Vaccine murine(H-$2^{d,p,u,q}$) [Shirai (1996)]

Vaccine: *Vector/type:* vaccinia *HIV component:* gp160

- Epitope name: HP53. Multiple murine MHC can cross-present this epitope, and P18, RIQRGPGRAFVTIGK, to specific CTL

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gp160(828–836)	gp41(829–837 LAI)	RVIEVLQRA	Vaccine	human(A2)	[Dupuis (1995)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- CTL from HLA-A2 positive subject react with this peptide

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gp160(828–836)	gp41(829–837 CM243 CRF01)	KVIEVAQGA	HIV-1 infection	human(A2)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested
- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by three amino acids, RVIEVLQRA
- This epitope was only conserved in CRF01 (subtype E), and identities were rare

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gp160(828–836)	Env(829–837 clade B)	RVIEVLQRA	Vaccine	human(A2.1)	[Kundu (1998a)]

Vaccine: *Vector/type:* recombinant protein *Strain:* MN *HIV component:* gp160

- Ten HIV-1+ HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual
- CTL responses after reimmunization may include recall responses – individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses

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gp160(830–854)	gp41(831–853)	IEVVQGAYRAIIRHIPR-RIRQGLERI	HIV-1 infection	human( )	[Price (1995)]

- Study of cytokines released by HIV-1 specific activated CTL

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gp160(835–843)	Env(834–842 SF2)	RAYRAILHI	HIV-1 infection	human(B*5101)	[Tomiyama (1999)]

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed
- This peptide could stimulate CTL from one person, however this CTL clone did not recognize B*5101 positive target cells infected with HIV-1 recombinant vaccinia expressing Env, so it was not confirmed that this peptide was a properly processed epitope

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gp160(837–856)	gp120(844–863)	YRAIRHIPRRIRQGLER-ILL	*in vitro* stimulation	human( )	[Lieberman (1995)]

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide

gp160(837–856)	gp120(844–863 SF2)	YRAIRHIPRRIRQGLER-ILL	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160
- One of these 11 had CTL response to this peptide
- The responding subject was HLA-A2, A26, B7, and B38

gp160(837–856)	gp120(844–863 LAI)	YRAIRHIPRRIRQGLER-ILL	HIV-1 infection	human(B35)	[Shankar (1996)]

gp160(837–856)	gp41(844–863 HXB2)	YRAIRHIPRRIRQGLER-ILL	HIV-1 infection	human(B8)	[Lieberman (1992)]

- CTL epitope defined by T-cell line and peptide mapping

gp160(842–856)	gp41( )	HIPRRIRQGLERALL	HIV-1 infection	human( )	[Altfeld (2001a)]

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses is underestimated if accessory proteins are not included in the study
- The only Env peptide recognized was gp41 HIPRRIRQGLERALL

gp160(843–851)	gp41(848–856 LAI)	IPRRIRQGL		human(B*0702)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*0702 epitope

gp160(843–851)	gp41(848–856 LAI)	IPRRIRQGL		human(B7)	[Brander & Walker(1995)]

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study

gp160(843–851)	( )	IPRRIRQGL	HIV-1 infection	human(B7)	[Soudeyns (1999)]

- Following primary infection, progressive diversification and accumulation of mutations of HIV-env nucleotide sequences was observed, focused in V2 in one individual and in V8 in another
- The patient with the V2 diversification showed only transient CTL against Env and Nef
- The patient with the V8 diversification had an immunodominant CTL response to V8 epitope IPRRIRQGL, and multiple escape variants emerged within a year: `--T------` and `--T-----F`, which abrogated the CT response *in vitro*, and also`----L---` and `-------D-` which gave diminished responses

gp160(843–851)	gp41(848–856 LAI)	IPRRIRQGL	HIV-1 infection	human(B7)	[Cao (1997)]

- The consensus peptide of clades A, B, D, and F is IPRRIRQGL
- The consensus peptide of clade C is IPRRIRQGF, and it is equally reactive

gp160(843–851)	gp41(848–856 clade B)	IPRRIRQGL	HIV-1 infection	human(B7)	[Wilson (1998b)]

- The extent of CTL interclade cross-reactivity from CTL isolated from individuals newly infected with B clade virus was studied, and extensive cross-reactivity was observed
- Two HLA B7 individuals had CTL response to B_LAI, A_92UG037 and C_92BR025 gp160, but were B clade strain MN non-responders – the authors note that the B7 epitope IPRRIRQGL is conserved between the LAI and clade A and C strains, but that MN has a non-conservative Arg to Thr substitution at position three that may be contributing to the specificity of the response in the HLA B7 individuals

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gp160(843–851)	gp41(843–851 HXB2)	IPRRIRQGL	HIV-1 infection	human(B7)	[Hay (1999)]

- CTL response to IPRRIRQGL was the immunodominant response in a rapid progressor – there was a subdominant response to SPAIFQSSM in Pol, and interestingly, no response to commonly immunodominant HLA A*0201 epitope SLYNTVATL, although this individual was HLA A*0201
- The individual showed a strong initial CTL response at the time of the initial drop in viremia, but it was quickly lost, although memory cells persisted
- Despite the initial narrow response to two epitopes, no other CTL responses developed
- No HIV-specific lymphoproliferative responses were detected in this patient, and neutralizing antibody response was weak
- Variants were observed *in vivo*, the most common form of the viral epitope at presentation at 3 months was the only form that did not elicit a CTL response: `----T----`; the other forms detected were `--------F`, `-----L--F`, `V-------F` and they could elicit a CTL response although the response to `-----L--F` was reduced
- A second rapid progressor had a detectable CTL response exclusively to this epitope

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gp160(843–851)	gp41( )	IPRRIRQGF	HIV-1 infection	human(B7)	[Cao (2000)]

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent-specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype
- This optimal epitope sequence, recognized by CTL derived from a Ugandan with an A subtype infection, is cross-reactive with subtypes A and B, but not in subtype D

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gp160(843–851)	gp41( )	IPRRIRQGL	HIV-1 infection	human(B7)	[Islam (2001)]

- Subject 053i was followed longitudinally from acute infection through death, and had rapid progression to AIDS
- This individual had a dominant response to IPRRIRQGL with strong *in vivo* activated responses and *in vitro* stimulated memory responses and a subdominant response to SPAIFQSSM – during the course of disease progression (4 Years), the functional CTL responses were lost and no sequence variation occurred within both epitopes

- At 3 months post-presentation, seven IPRRIRQGL CTL clones were obtained, five used the T-cell receptor Vβ 6S1 and Jβ 2.7 and had the CDR3 WAASS, two used Vβ16S1, ERSPPGD, Jβ 2.7 and one CTL clone isolated at 39 months was Vβ 14S1, CR3 PTAAG, and Jβ 2.1 – all of these clones persisted over the course of the infection, even to time of death, despite the loss of CTL functional responses over time

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gp160(843–851) gp41(843–851 SF2) IPRRIRQGL HIV-1 infection human(B7) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 2/4 group 1, 1/3 group 2, and 1/1 group 3

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gp160(843–851) gp41(848–856) IPRRIRQGL HIV-1 exposed seronegative, HIV-1 infection human(B7) [Kaul (2001a)]

- IPRRIRQGL cross-reacts with clades A, B and D
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B7 women, 2/5 HEPS and 5/6 HIV-1-infected women recognized this epitope
- The dominant response to this HLA allele was to this epitope in 2 of the 5/6 HIV-1-infected women that responded to the epitope, but in neither of the 2/5 HEPS cases
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV

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gp160(843–851) gp41(843–851) IPRRIRQGL HIV-1 infection human(B7) [Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes

- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope

gp160(843–851)	gp41( )	IPRRIRQGL	HIV-1 infection	human(B7)	[Altfeld (2000)]
	• This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual				
gp160(845–856)	gp41(852–863 HXB2)	RRIRQGLERILL	HIV-1 infection	human(A30, B8)	[Lieberman (1992)]
	• CTL epitope defined by T-cell line and peptide mapping				
gp160(845–856)	gp41(852–863 LAI)	RRIRQGLERILL	HIV-1 infection	human(B7)	[Shankar (1996)]

Table 19: **Env**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Env(306–322)	gp160( )	SIRIQGPGRAFVTIGI	Vaccine	murine(H-2D^d)	[Deml (1999)]
Vaccine: *Vector/type:* recombinant protein *Strain:* LAI *HIV component:* gp160 *Stimulatory Agents:* CpG oligodeoxynucleotide, alum					
• Addition of CpG oligodeoxynucleotide to a gp160/alum vaccine given to BALB/c mice shifted the response to Th0/Th1 from Th2, but no still CTL response to this immunodominant epitope was induced					
Env( )	gp160( )		Vaccine	human( )	[Belshe (1998)]
Vaccine: *Vector/type:* canarypox prime with rgp120 boost *Strain:* MN, LAI, SF2 *HIV component:* gp120, gp41, Gag, Protease					
• The live canarypox vaccine ALVAC-HIV(vCP205) carrying MN gp120, LAI gp41, Gag and Protease, and boosted with SF-2 rpg120, was given to HIV-1 seronegative volunteers – HIV-specific Env or Gag CD8+ CTL were detected in 64% of the volunteers					
Env( )	gp160( )		HIV-1 infection	human( )	[Zheng (1999)]
• Protein delivery (gp160 LAV, p66 LAV, and p24 NY5) to human dendritic cells (DC) with liposomes provides enhanced memory CTL response relative to delivery of protein alone					
• Chloroquine administration enhanced epitope presentation, and brefeldin A and peptide aldehyde inhibitors inhibited antigen presentation, suggesting epitopes were processed by a classical proteasome pathway					
Env( )	Env( )		HIV-1 infection	human( )	[Wasik (2000)]
• HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of IL-2, as well as β-chemokines, relative to other HIV+ infants					
• No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors					
• CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccinia/HIV constructs					
Env( )	gp120( )		HIV-1 infection	human( )	[Soudeyns (2000)]
• Analysis of T-cell receptor β-chain variable region repertoire indicates that antiretroviral therapy (ART) and highly active antiretroviral therapy (HAART) decrease global CD8 T-cell oligoclonality during primary HIV infection					
• A sharp decline in HIV-1 gp120-specific CTL clones was observed in HAART-treated subjects					
Env( )	Env( )		Vaccine	human( )	[Salmon-Ceron (1999)]
Vaccine: *Vector/type:* canarypox *Strain:* LAI, MN *HIV component:* gp41, Gag, Pro, V3					
• The vaccine used was a rec canarypox with HIV-1 gp120 MN, tm/gag/protease LAI (vCP205), alone or with p24E-V3 MN synthetic peptide (CLTB-36))					
• Twenty HIV negative subjects were vaccinated in phase I trial with combinations of vCP205 and CLTB-36					

- Immunization with vCP205 induced HIV-1-specific ABs to gp160, V3, and p24 antigens, and CTL immune responses against vCP205 were detected after the fourth immunization in 33% of the subjects against Env, Gag and Pol, but the CLTB-36 peptide did not produce AB or CTL immune responses against p24 or gp160

Env( ) Env( ) HIV-1 infection human( ) [Gamberg (1999)]

- 13/13 subjects with advanced HIV infections showed CD8 T-cell proliferation and differentiation of CTL *in vitro*, and six individuals showed HIV-specific responses to Gag, Pol, Env or Nef antigens
- Data suggests that the functional and genetic integrity of the CD8 T-cell repertoire (TCR betaV gene intrafamily genetic diversity) remains intact through advanced HIV infection, although HIV-specific CTL activity decreases

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Env( ) Env( ) Vaccine human( ) [Gorse (1999)]

Vaccine: *Vector/type:* canarypox prime with rgp120 boost *Strain:* LAI and SF2 *HIV component:* Env, Gag, Pro, Nef, Pro

- The vaccine used was rec canarypox expressing HIV-1 env, gag, pol, nef and protease (vCP300) with or without administration of HIV-1 SF-2 rgp120
- In vitro inducible CTL activity against HIV-1 Env, Gag, Pol, and Nef antigens was observed in 79% (15/19) of vaccine recipients
- The combination of vCP300 and vP1291 together resulted in an overall increase in CTL induction and detection sensitivity

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Env( ) Env( ) HIV-1 infection human( ) [Buseyne (1998b)]

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes

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Env( ) gp120( ) Vaccine Rhesus macaque( ) [Shiver (1997)]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* gp120, gp160

- DNA vaccinations of Rhesus monkeys with a gp120 or gp160 DNA vaccine elicited a strong CD8 cytotoxic T-cell response

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Env( ) gp160( ) polyclonal HIV-1 infection Macaca nemestrina( ) [Kent (1997b)]

- Macaques can be infected with HIV, and clear the infection within 6 months, so it is of interest to examine their initial immune response
- A strong CTL response against env, pol and gag antigens can be detected
- The CTL response peaked by 4 weeks and declined dramatically by 8 weeks
- The response in the lymph nodes and peripheral blood was comparable

---

Env( ) gp160( ) Vaccine murine( ) [Kim (1997b)]

Vaccine: *Vector/type:* DNA *HIV component:* Gag, Pol, Vif, Env *Stimulatory Agents:* B7, IL-12

- A gag/pol, vif or env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice
- When IL-12 was present, CTL response could be detected even without *in vitro* stimulation

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Env( )	gp160( )		Vaccine	murine( )	[Kim (1997c)]

Vaccine: *Vector/type:* DNA *HIV component:* Gag, Pol, Vif, Env *Stimulatory Agents:* B7, IL-12

- A gag/pol or env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules CD86, gave a dramatic increase in both the cytotoxic and proliferative responses in mice
- When CD86 was present, CTL response could be detected even without *in vitro* stimulation

---

Env( )	gp120( )	polyclonal	Vaccine	Rhesus macaque( )	[Letvin (1997)]

Vaccine: *Vector/type:* DNA prime with rgp160 boost *Strain:* HXBc2 *HIV component:* gp160

- Vaccination of Macaques mulatta (Rhesus monkeys) with an HXBc2 env DNA prime and a protein boost elicited a T-cell proliferative response, a CTL response, and type-specific neutralizing antibodies
- Vaccinated animals challenged with SHIV-HXB2 were protected from infection

---

Env( )	gp120( )	polyclonal	Vaccine	human( )	[MacGregor (1998)]

Vaccine: *Vector/type:* DNA *Strain:* MN *HIV component:* Env, Rev

- An HIV DNA env and rev vaccine given to 15 asymptomatic HIV+ individuals at three different dosages, 30, 100 or 300 ug, was safe
- The CTL response to gp120 was enhanced in 0/4 patients in the 30 μg group, 2/3 patients in the 100 μg group, and 0/3 in the 300 μg group – but the non-responding patients in the 300 μg group had a strong CTL response prior to vaccination, and the CTL results are inconclusive

---

Env( )	gp120( )		HIV-1 infection	human( )	[Trickett (1998)]

- Twelve HIV-1 infected patients were re-infused with their own lymphocytes, cryopreserved from an earlier time point in the infection
- Improvement in CD4+ and CD8+ T-cells was seen in 7/12, and an increase in the CTL response to Env was seen in one patient

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Env( )	gp120( )		HIV-1 infection	human( )	[Legrand (1997)]

- Seventeen recently infected patients were tested for CTL response to HIV proteins Env, Gag, Pol, Rev, Nef, Vif and Tat
- An early response (within a month following PI) was noted in 87% of the subjects to Gag, 75% to Env, and 50% to Nef
- Early responses to Pol, Rev, Vif and Tat were rare

Env( )	gp120( )		Vaccine	human( )	[Corey (1998)]

Vaccine: *Vector/type:* vaccinia prime with rgp120 boost *Strain:* LAI, SF2, MN *HIV component:* gp160

- Vaccinia-naive subjects were vaccinated with vaccinia-gp160 LAI and boosted with gp120 SF2, LAI, MN, or 160 MN
- 26/51 had an anti-Env CTL response, and those that were boosted with gp120 tended to produce Abs that neutralized autologous laboratory strains with some cross-reactivity

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Env( )	Env( )		HIV-1 infection	human( )	[Betts (1997)]

- 6/8 individuals from Zambia infected with C clade virus had CTL that were able to make response to B clade HIV-1 IIIB vaccinia-expressed Gag, Pol and Env proteins
- A vigorous cross-clade response was not limited to a particular protein, and the level of recognition of different proteins varied among the six patients

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Env( ) Env( ) HIV-1 infection human( ) [De Maria (1997)]

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T-cell function
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels

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Env( ) Env( ) HIV-1 infection human( ) [Betts (1999)]

- This study demonstrated an inverse correlation between HIV Type I plasma viral load and CTL activity directed against HIV-1 Pol, and stronger combined effects of Pol- and Env-specific CTL, in long-term survivors (LTS) of HIV-1 infection

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Env( ) Env( ) HIV-1 infection human( ) [Buseyne (1998a)]

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants and: remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load

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Env( ) Env( ) HIV-1 exposed seronegative human( ) [Goh (1999)]

- 13/37 exposed uninfected individuals with repeated high-risk sexual exposure had HIV-1 specific CTL against Env, Gag, Pol, or a combination of proteins – CTL activity was correlated with a CCR5 wildtype genotype
- In this group, the highest CTLp frequencies were directed at Gag, but the most common response was to Env and four individuals had responses to multiple HIV-1 proteins

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Env( ) Env( ) Vaccine human( ) [Evans (1999)]

Vaccine: *Vector/type:* canarypox *HIV component:* gp120, gp41, Gag, Pro, Nef, RT

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination

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Env( ) Env( ) Vaccine Macaca nemestrina( ) [Kent (1998)]

Vaccine: *Vector/type:* DNA prime with vaccinia boost *Strain:* LAI *HIV component:* Env, Gag

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T-cell immunity than either vaccine alone
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env. The T help response happened despite a decrease in antibody titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced

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Env( ) Env( ) Vaccine human( ) [Salmon-Ceron (1999)]

Vaccine: *Vector/type:* canarypox *Strain:* MN, LAI *HIV component:* gp120, gp41, Gag, Protease

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy, uninfected volunteers

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Env( ) Env( ) Vaccine chimpanzee( ) [Kim (1998)]

Vaccine: *Vector/type:* DNA *HIV component:* Env, Gag, Pol *Stimulatory Agents:* CD86, CD80

- The study explores the use of co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses

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Env( ) gp120( ) Vaccine Rhesus macaque( ) [Notka (1999)]

Vaccine: *Vector/type:* Semliki-Forest Virus with virus-like particle boost *Strain:* IIIB *HIV component:* gag, gp120

- Immunization of SIV Pr56Gag-derived VLPs with HIV-1 gp120 anchored on their surface induced Abs, CTL and Th responses to HIV gp120; priming with the HIV antigens in Semliki-Forest Viruses enhanced the immunological outcome
- Immunized monkeys challenged with SHIV showed a more rapid reduction of plasma viremia

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Env( ) Env( ) HIV-1 exposed seronegative human( ) [Akridge (1999)]

- This study suggests that HIV-1-resistance in exposed and uninfected individuals is not only associated with the 32-bp deletion in the HIV-1 co-receptor CCR5, but can be related to HIV-1 specific CTL immunity

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Env( ) gp120( ) HIV-1 infection human( ) [Aladdin (1999)]

- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death

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Env( ) gp120( ) HIV-1 infection human( ) [Aladdin (2000)]

- The administration of IL-2 caused an initial enhancement of CD4 cell counts that was accompanied by a decrease in CTL activity – IL-2 therapy did not reduce initial HIV viral load and viral replication was ultimately enhanced

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Env( ) Env( ) HIV-1 infection human( ) [Jin (1998a)]

- CTL precursor frequencies were determined in HIV-1 infected pregnant women, and higher CTLp frequencies to Pol and SF2 Nef, but not IIIB Nef, were found in non-transmitting mothers than in transmitting mothers – Nef CTL responses have been found in uninfected infants born to HIV+ women (Lazuriaga95);
- Very different CTLp frequencies were observed in env depending on whether IIIB, MN, RF, BK, or SF2 was used as antigen – no association between env specific CTL and transmission was observed

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Env( ) Env( ) Vaccine ( ) [Zavala (2001)]

Vaccine: *Vector/type:* vaccinia *HIV component:* Env

- This paper is a review of vaccinia in the context of vaccines strategies that use different vectors to prime and boost, and emphasizes a unique capacity of vaccinia to very efficiently boost memory T-cell responses
- HIV is discussed in the context of Gonazalo *et al.* 1999, where a V3 CTL epitope expressed in reFlu was boosted most effectively by vaccinia expressing the full Env

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Env( ) Env( ) Vaccine Rhesus macaque( ) [Akahata (2000)]

Vaccine: *Vector/type:* DNA *Strain:* ZF1 *HIV component:* complete genome

- Rhesus macaques were vaccinated by i.m. injection with naked plasmid DNA carrying an HIV-1 complete genome vaccine, strain ZF1, with a mutated zinc finger in the nucleocapsid to prevent packaging
- Env and Gag specific CTL, but no antibody responses, were induced in 2/4 vaccinated monkeys (MM145 and MM153)
- 2/4 monkeys (MM146 and MM143) produced antibodies against p24 and/or gp160, but no CTL response
- PBMC from all vaccinated monkeys produced IFN-γ, in response to HIV-1 gp160, indicating a Th response – this response was 5 times higher in MM145, the animal with the strongest CTL response
- 4 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM145 and MM153 (with a homologous Env) decreased to near or below the detection limit
- 6-8 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM146 and MM143 decreased near or below the detection limit

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Env( ) gp120( ) none HIV-1 infection human( ) [Young (2001)]

- Addition of recombinant human IL-12 (rhIL-12) to cultures increased HIV-specific lysis of HIV-Gag, Pol and gp120 vaccinia expressed antigens (11/15 tested increased lysis by > 5%) if the culture was derived from HIV+ individuals who had > 500 CD4 cells/μl
- 2/10 individuals with <200 CD4 cells/μl, and 3/10 individuals with 200-500 CD4 cells/μl, had an increase of >5% upon treatment of the culture with rhIL-12, so a few individuals in late stage disease had CD8 cells that maintained responsiveness to rhIL-12

Env( ) Env( ) HIV-1 infection human( ) [Cao (2000)]

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent-specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype

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Env( ) Env( ) Vaccine human( ) [AIDS Vaccine Evaluation Group 022 Protocol Team(2001)]

Vaccine: *Vector/type:* canarypox, recombinant protein *Strain:* MN (gp120), LAI (gp120, protease and gag), and SF2 gp120 *HIV component:* Env, Gag, Protease *Stimulatory Agents:* MF-59 adjuvant

- 26/42 subjects who received CP vac-env-pro vaccine had a CTL response measured by Cr-release, while only 3/17 who were vaccinated with rec gp120 had a CTL response
- A combination of a CP vac-env-pro vaccine with rec gp120 gave CD8+ T-cells in 62% of subjects, and NAbs in 91% of subjects

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Env( ) Env( ) HIV-1 infection human( ) [White (2001)]

- HIV-specific CTL activity was detected in the female reproductive tract of only 1/3 HIV-infected women who underwent a hysterectomy, although CTL could be identified in the PBMC of all three women

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Env( )	Env( )	HIV-1 infection	human( )	[Jin (2000a)]

- The CTL precursor level (CTLp) was measured in long term non-progressors (LTNP) with low viral load using limiting dilution analysis and measuring CTL against Env Gag and Pol expressed in vaccinia in autologous targets
- LTNPs have high memory CTL numbers and low viral load

Env( )	Env( )	HIV-1 infection	human( )	[Jin (2000a)]

- The CTL effector levels (CTLe) were compared in long term non-progressors (LTNP) with low viral load and in patients whose virus was well-suppressed by therapy, using a tetramer assay
- LTNPs have high memory CTLe numbers and low viral load, while HAART patients had low CTLe numbers and low viral load

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Env( )	Env( )	HIV-1 exposed seronegative	human( )	[Rowland-Jones (2001)]

- This is a review that summarizes observations about HIV-specific CTL found in the HIV-1 exposed persistently seronegative (HEPS) population
- The CTL responses assayed by ELISPOT and by CTL precursor frequencies by limiting dilution analysis indicate that CTL in HEPS individuals tend to be of a lower magnitude than in chronic HIV-1 infections – the responses in HEPS cases are below the level of detection by tetramer assays
- CD8+ CTL responses tend to be detectable in HEPS subjects only if they are recently exposed, and the response diminishes if exposure is reduced – it is not clear if there is a stable memory population in HEPS cases
- CD8+ CTL responses in the HEPS population are associated with HIV-1 specific CD4+ T-cell responses, assayed by proliferation assays, IL-2 secretion, and ELISPOT, and the authors consider the possibility that HIV-1-specific T-help responses improve the "quality" of the CD8+ response in HEPS individuals relative to HIV-1 infected individuals, who tend to have a poor HIV-1-specific T-help response
- HIV-1 specific CD8+ CTL responses in HIV-1 infected individuals show reduced levels of perforin, and the T-cells may not mature properly, and although similar studies have not been conducted in HEPS individuals this is considered as a possible difference in the CTL immune response in HEPS and HIV-1 infected people

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Env( )	gp41(842–850 IIIB BH8)	HIV-1 infection	human(B7)	[Pantaleo (1997), Soudeyns & Pantaleo(1997)]

- Clonotype-specific PCR and analysis of *in vivo* HIV-specific CTL showed that in early infection HIV-specific CTL clones preferentially accumulate in blood rather than lymph nodes and that they accumulate prior to down-regulation of virus

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Env( )	Env( )	Vaccine	murine(H-2^d)	[Ishii (1997)]

Vaccine: *Vector/type:* DNA with CMV promotor with cationic liposome *HIV component:* gp160, Rev

- pCMV160/Rev is a DNA vaccine candidate carrying gp160 and Rev linked to a cytomegalovirus (CMV promotor)

Env( )	gp160( )	Vaccine	murine(H-2^d)	[Vinner (1999)]

Vaccine: *Vector/type:* DNA *Strain:* MN *HIV component:* gp160, gp120, codon-optimized

- Mammalian codon optimization renders gp160 expression Rev independent, increases gp160 expression levels, and DNA vaccination of BALB/c mice yields a higher antibody response with an earlier onset than wild type

- Secreted gp120 gave higher antibody titers than membrane bound gp160
- In contrast to antibodies, synthetic codon-optimized DNA did not alter the CTL response, wild type genes generated equally strong CTL responses

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Env( ) ( ) Vaccine murine(H-2^d) [Kato (2000)]

Vaccine: *Vector/type:* peptide *HIV component:* V3 *Stimulatory Agents:* Cholera Toxin adjuvant, IL-4, GMCSF

- A multicomponent peptide vaccine VC1 with cholera toxin adjuvant was given to mice.
- Immunization of BALB/c mice with VC1 and CT induced a strong CTL response which was enhanced by IL-12 expressing plasmids
- Immunization with VC1 and CT resulted in HIV-1 specific IgA antibody responses, which were increased by the combination of IL-4 or GM-CSF expressing plasmids

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Env( ) gp160( ) Vaccine murine(H-2^d) [Kaneko (2000)]

Vaccine: *Vector/type:* DNA *Strain:* IIIB *HIV component:* gp160 *Stimulatory Agents:* PLG-microparticle

- A PLG-microparticle encapsulated DNA encoding gp160 was given to mice.
- Oral DNA vaccination of BALB/c mice induced mucosal and systemic gp160 glycoprotein-specific cellular and humoral immune responses, and mice vaccinated orally had higher resistance to HIV-env expressing vaccinia intrarectal challenge than mice vaccinated i.m.

Env( ) Env( ) Vaccine murine(H-2^d) [Xin (2001)]

Vaccine: *Vector/type:* adeno-associated virus (AAV) *HIV component:* Env, Tat, Rev *Stimulatory Agents:* IL-2

- An AAV vector expressing HIV-1 env, tat, and rev genes (AAV-HIV vector) was used to vaccinate BALB/c mice
- A single injection stimulated and long lasting serum IgG, fecal IgA, and HIV-specific CTL
- Boosting enhanced the humoral response, and IL-2 enhanced T-cell immunity

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Env( ) Env( ) Vaccine murine(H-2^d) [Gonzalo (1999)]

Vaccine: *Vector/type:* influenza, vaccinia *Strain:* IIIB *HIV component:* V3, Env

- The use of two different live vectors for priming and boosting has a synergistic effect on the immune response against HIV-1 – a 5-6 fold enhanced CTL response in Balb/c mice occurred when they were immunized with rec influenza virus (Flu-Env) expressing the V3 loop epitope from HIV-1 strain IIIB, and boosted with a vaccinia virus recombinant (VV-Env) expressing the complete HIV-1-IIIB env protein, comared to either immunogen alone

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Env( ) Env( ) none Vaccine murine(H-2^d) [McGettigan (2001)]

Vaccine: *Vector/type:* rabies virus *Strain:* NL4-3, 89.6 *HIV component:* gp160

- BALB/c were immunized with a replication competent recombinant rabies virus (RV) vaccine expressing HIV-1 gp160
- A single vaccination induced induced strong and long-lasting (4.5 months) gp160-specific CTL cytotoxic responses
- Although the greatest specific lysis was achieved when the vaccine strain was also used as the *in vitro* the target strain to assess the response, there was extensive CTL cross-reactivity against other B clade HIV-1 envelope proteins, implying CTL recognition of multiple epitopes within the HIV-1 envelope protein

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Env( )	Env( )	SIV Nef and Env CTL epitopes	SIV infection	Rhesus macaque(Mamu-A*11, -B*03, -B*04, and -B*17)	[Dzuris (2000)]

- Cell binding assays for Mamu molecules were employed to describe the peptide binding motifs for Mamu-A*11, -B*03, -B*03, -B*04, and -B*17 CTL epitopes – a similarity for Mamu-A*11 and -B*03 and human HLA-B*44 and -B*27, respectively, was observed – all epitopes studied were SIV epitopes, so not specifically listed here

Env( )	gp120(303–327)	HIV-1 infection	human(A2, A3, A11, B27)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles
- For this cluster of epitopes spanning the tip of the V3 loop, they suggest including a sequence from each clade

Table 20: **Nef**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Nef(13–20)	Nef(13–20 LAI)	WPTVRERM	HIV-1 infection	human(B*0801)	[Brander & Goulder(2001), Goulder (1997g)]
	• C. Brander notes this is a B*0801 epitope				
Nef(13–20)	Nef(13–20 LAI)	WPTVRERM	HIV-1 infection	human(B8)	[Goulder (1997g)]
	• Unusual epitope for HLA-B8, but compatible with crystal structure predictions				
Nef(13–20)	Nef(13–20)	WPTVRERM	HIV-1 infection	human(B8)	[Betts (2000)]
	• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant • Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes • 1/11 of the HLA A2+ was HLA A*0201, A31, B8, B51 and responded to this epitope as well as seven others				
Nef(13–20)	Nef(13–20 SF2)	WPTVRERM	HIV-1 infection	human(B8)	[Altfeld (2001c)]
	• Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection • The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef • Previously described and newly-defined optimal epitopes were tested for CTL response • Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 1/3 group 1, 0/3 group 2, and 1/2 group 3				
Nef(13–20)	Nef(13–20)	WPTVRERM	HIV-1 infection	human(B8)	[Day (2001)]
	• B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual				
Nef(42–50)	Nef(44–52 HXB3)	ALTSSNTAA	Vaccine	murine(HLA-A201 transgenic)	[Sandberg (2000)]
	Vaccine: *Vector/type:* DNA, peptide *Strain:* HXB3 *HIV component:* Nef *Stimulatory Agents:* Freund's adjuvant • Ten Nef 9-mer peptides were predicted to have a strong binding affinity with HLA-A*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly • A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with either nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by gene gun • ALTSSNTAA was also tested by subcutaneous injection of Nef peptides in Freund's adjuvant • ALTSSNTAA bound weakly to HLA-A2, but it had the strongest CTL response among the three elicited by the DNA vaccine and a strong response to the peptide vaccination				

Nef(62–81)	Nef(61–80)	EEEEVGFPVTPQVPLR-PMTY	*in vitro* stimulation	human( )	[Lieberman (1995)]

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide

Nef(62–81)	Nef(61–80 SF2)	EEEEVGFPVTPQVPLR-PMTY	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI Nef
- Two of these 12 had CTL response to this peptide
- The responding subjects were HLA-A11, A24, B8, B35, and HLA not determined

Nef(62–81)	Nef(61–80 SF2)	EEEEVGFVTPQVPLRP-MTY	HIV-1 infection	human( )	[Lieberman (1997b)]

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients

Nef(62–81)	Nef( )	EEEEVGFPVTPQVPLR-PMTY	HIV-1 infection	human( )	[Altfeld (2001a)]

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses is underestimated if accessory proteins are not included in the study
- Nef peptides PQVPLRRMTYKAAVDLSHFL, KAAVDLSHFLKEKGGLEGLI and EEEEVGFPVTPQVPLRPMTY were recognized and the first two share KAAVDLSHFL (a Cw8 epitope), the first and last share PQVPLRPMTY

Nef(66–80)	Nef(66–80 BRU)	VGFPVTPQVPLRMT	HIV-1 infection	human(A1, B8)	[Hadida (1992)]

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients

Nef(66–80)	Nef(64–78)	VGFPVTPQVPLRMT	HIV-1 infection	human(A1, B8)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

Nef(66–97)	Nef(66–97 LAI)	VGFPVTPQVPLRPMT-YKAAVDLSHFLKEKGG-L	Vaccine	human( )	[Gahery-Segard (2000)]

Vaccine: *Vector/type:* lipopeptide *HIV component:* six peptides

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 5/10 reacted to this Nef peptide
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual

	• 5/12 tested had an IgG response to this peptide				
Nef(68–76)	Nef(72–80 SF2)	FPVRPQVPL	HIV-1 infection	human(B*3501)	[Tomiyama (1997)]
	• A CTL clone responsive to this epitope was obtained • 3/7 B35-positive individuals had a CTL response to this epitope • An R to T substitution at position 4 abrogates specific lysis, but not binding to B*3501				
Nef(68–76)	Nef(72–80)	FPVRPQVPL	HIV-1 infection	human(B*3501)	[Tomiyama (2000a)]
	• CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A • A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals • CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm • The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)				
Nef(68–76)	Nef(72–80 SF2)	FPVRPQVPL	HIV-1 infection	human(B*3501)	[Shiga (1996)]
	• Binds HLA-B*3501				
Nef(68–76)	( )	FPVRPQVPL	HIV-1 infection	human(B35)	[Kawana (1999)]
	• HLA B35 is associated with rapid disease progression • The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals • 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation				
Nef(68–76)	Nef(66–74)	FPVRPQVPL	HIV-1 infection	human(B35)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
Nef(68–76)	Nef(68–76)	FPVTPQVPL	*in vitro* stimulation	human(B7)	[Wilson (1999b)]
	• Dendritic cells are the most potent for priming T-cell responses – DCs can stimulate autologous CTL responses from T-cells cultured from HIV negative donors • Th1-biasing cytokines IL-12 or IFNα enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within • B7 and A2 Nef epitopes were studied – FPVTPQVPL has a high affinity for B7				
Nef(68–76)	Nef(68–76)	FPVTPQVPL	HIV-1 infection	human(B7)	[Day (2001)]
	• The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP) • Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person				

- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope

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Nef(68–77) Nef(68–77 LAI) FPVTPQVPLR HIV-1 infection human(B*0702) [Brander & Goulder(2001)]

- C. Brander notes this is a B*0702 epitope

Nef(68–77) Nef(68–77 LAI) FPVTPQVPLR HIV-1 infection human(B7) [Haas (1996)]

- There was a high degree of variation in three CTL epitopes in Nef in four slow and non-progressors, and variant specific CTLs arose over time to eliminate variants, indicating immune selection

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Nef(68–77) Nef( ) FPVTPQVPLR HIV-1 infection human(B7) [Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- FPVTPQVPLR was recognized in 1 of the 6 women (ML1203), and the response was present in the last available sample prior to seroconversion, 7 months
- 20/20 sequences of the infecting strain had no substitutions in this epitope, all were FPVTPQVPLR, so there was no evidence for escape
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope was recognized in 1/22 HEPS sex worker controls, ML851

Nef(68–77) Nef(66–75) FPVRPQVPLR HIV-1 infection human(B7) [Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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Nef(68–77) Nef(68–77 SF2) FPVTPQVPLR HIV-1 infection human(B7) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3

Nef(68–77) Nef(68–77) FPVTPQVPLR HIV-1 exposed seronegative, HIV-1 infection human(B7) [Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV

Nef(68–77)	Nef(68–77)	FPVTPQVPLR	HIV-1 infection	human(B7)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope

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Nef(68–84)	Nef( )	FPVRPQVPLRPMTYK-GA		human( )	[Jubier-Maurin (1999)]

- 41 new HIV-1 strains describing envelope subtypes of HIV-1 A-H were genetically characterized in the nef coding region – 34 subtypes were classified in the same subtype in nef and env and 7 of the 41 strains were recombinants
- This region was defined as a CTL epitope region that is conserved among HIV-1 M group subtypes

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Nef(69–79)	( )	RPQVPLRPMTY	HIV-1 infection	human(B35)	[Kawana (1999)]

- HLA B35 is associated with rapid disease progression
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals – only one of these reduced the binding of the peptide to B35 and was shown to be an escape mutation
- ----------F was found in 9/10 of the B35+ individuals, none of the B35- individuals – the Y –> F substituted peptide had a similar binding affinity with B35 and was recognized by a CTL clone equally with wildtype

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Nef(71–79)	Nef(71–79 LAI)	TPQVPLRPM	HIV-1 infection	human(B*0702)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*0702 epitope

Nef(71–79)	Nef(71–79 SF2)	TPQVPLRPM	HIV-1 infection	human(B7)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3

Nef(71–79)	Nef(71–79)	TPQVPLRPM	HIV-1 infection	human(B7)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope

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Nef(71–81)	Nef(75–85 SF2)	RPQVPLRPMTY	HIV-1 infection	human(B*3501)	[Tomiyama (1997)]

- A CTL clone responsive to this epitope was obtained
- 4/7 B35-positive individuals had a strong CTL response to this epitope
- An R to T substitution at position 1 abrogates specific lysis, but not binding to B*3501
- An R to H substitution at position 7 did not alter reactivity

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Nef(71–81)	Nef(75–85)	RPQVPLRPMTY	HIV-1 infection	human(B*3501)	[Tomiyama (2000a)]

- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

Nef(71–81)	Nef(75–85 SF2)	RPQVPLRPMTY	HIV-1 infection	human(B*3501)	[Shiga (1996)]

- Binds HLA-B*3501

Nef(71–81)	Nef(69–79)	RPQVPLRPMTY	HIV-1 infection	human(B35)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

Nef(72–79)	Nef( )	VPLRPMTY	HIV-1 exposed seronegative	human(B35)	[Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells
- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women

Nef(72–79)	Nef( )	VPLRPMTY	HIV-1 infection	human(B35)	[Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

Nef(72–91)	Nef(71–90 SF2)	PQVPLRMTYKAAVDL-SHFL	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef
- Three of these 11 had CTL response to this peptide
- The responding subjects were HLA-A3, A32, B51, B62; HLA-A11, A24, B8, B53

Nef(72–91)	Nef(71–90 SF2)	PQVPLRPMTYKAAVD-LSHFL	HIV-1 infection	human( )	[Lieberman (1997b)]

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients

Nef(72–91)	Nef( )	PQVPLRRMTYKAAVD-LSHFL	HIV-1 infection	human( )	[Altfeld (2001a)]

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses is underestimated if accessory proteins are not included in the study
- Nef peptides PQVPLRRMTYKAAVDLSHFL, KAAVDLSHFLKEKGGLEGLI and EEEEVGFPVTPQVPLRPMTY were recognized and the first two share KAAVDLSHFL (a Cw8 epitope), the first and last share PQVPLRPMTY

Nef(73–82)	Nef(73–82)	QVPLRPMTYK	HIV-1 infection	human( )	[Garcia (1997)]

- The anti-Nef CTL line P1 specific for this epitope is able to kill target cells via two mechanisms
- First: Ca^{2+}-dependent, perforin-dependent Nef-specific lysis
- Second: Ca^{2+}-independent, CD95-dependent apoptosis that could also kill non-specific targets
- Findings indicate that the two mechanisms are not mutually exclusive in human CTL, as they are in mice
- CTL mediated CD95-dependent apoptosis may play a role in pathogenesis

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Nef(73–82)	Nef(73–82 NL43)	QVPLRPMTYK	HIV-1 infection	human(A*0301)	[Koenig (1990)]

- 81 Tyr is critical for binding to A3.1
- C. Brander notes that this is an A*0301 epitope in the 1999 database

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Nef(73–82)	Nef(73–82 LAI)	QVPLRPMTYK		human(A*0301)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*0301 epitope

Nef(73–82)	Nef(73–82)	QVPLRPMTYK	HIV-1 infection	human(A11)	[Le Borgne (2000)]

- Soluble factors in supernatant from both an HIV-specific cloned CTL line and an EBV (Epstein-Barr-virus) CTL line inhibit viral replication, but do not block viral entry in CD4+ T lymphocytes, by a noncytotoxic mechanism

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Nef(73–82)	Nef(73–82 LAI)	QVPLRPMTYK	HIV-1 infection	human(A11)	[Robertson (1993)]

- Development of a retroviral vector (pNeoNef) to generate autologous CTL targets
- [Hunziker1998] suggests that HLA-A2 does not in fact present this epitope
- The initial assignment of HLA-A2 presentation for this epitope was based on a serological HLA typing. Subsequently, the authors revisited the issue with genetic HLA typing and found that HLA-A11 was the correct presenting molecule (Dr. Florence Buseyne, Pers. Comm., 2000)

Nef(73–82)	Nef(73–82 LAI)	QVPLRPMTYK	HIV-1 infection	human(A11)	[Couillin (1994), Goulder (1997a)]

- Mutational variation in HIV epitopes in individuals with appropriate HLA types can result in evasion of CTL response
- [Goulder (1997a)] is a review of immune escape that summarizes this study

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Nef(73–82)	Nef(73–82 LAI)	QVPLRPMTYK	HIV-1 infection	human(A11)	[Couillin (1995)]

- Mutations found in this epitope in HLA-A11 positive and negative donors were characterized

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Nef(73–82)	( )	QVPLRPMTYK		(A11)	[Brander & Goulder(2001), Buseyne(1999)]

Nef(73–82)	Nef(73–82)	QVPLRPMTYK	HIV-1 infection	human(A11)	[Oxenius (2000)]

- Epitope name: QVP. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- One of the 2/8 HLA-A11 study subjects recognized this CTL epitope
- Patient SC18(HLA A2/11, B8/44, Cw06/0701, DR3/7, DR52/53, DQ2) recognizes the epitopes ACQGVGGPGHK, QVPLRPMTYK, AVDLSHFLK, and one called QIY but not fully described – he had brief therapy upon seroconversion and has had low viral load during 600 days of follow up

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Nef(73–82)	Nef(73–82)	QVPLRPMTYK	HIV-1 exposed seronegative, HIV-1 infection	human(A11)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

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Nef(73–82)	Nef(73–82)	QVPLRPMTYK	HIV-1 infection	human(A11)	[Appay (2000)]

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV
- HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

Nef(73–82)	Nef(71–80 93TH253 CRF01)	QVPLRPMTYK	HIV-1 exposed seronegative, HIV-1 infection	human(A11)	[Sriwanthana (2001)]

- Epitope name: N73-82. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was weakly reactive in HEPS study subjects 265 who was HLA A2/A11 and 128 who was HLA A11/A33, and after a second *in vitro* stimulation, in study subject 256 who was HLA A11/33, making it the most reactive epitope tested in HLA-A11 HEPS women, with 3/4 responding
- This epitope was strongly reactive in HIV+ study subject 053 who carried HLA-A11

Nef(73–82)	Nef(71–80 93TH253 CRF01)	QVPLRPMTYK	HIV-1 infection	human(A11)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified

- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined
- 4/8 tested FSWs recognized this epitope
- An HLA-A11 tetramer was made for this epitope, which was recognized by two subjects – only one subject had an expanded tetramer staining T-cell population after *in vitro* stimulation
- This epitope was highly conserved in other subtypes, and exact matches were common

Nef(73–82)	Nef(73–81)	QVPLRPMTYK	HIV-1 infection	human(A2, A3, A11, B35)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

Nef(73–82)	Nef(73–82 LAI)	QVPLRPMTYK	HIV-1 infection	human(A3)	[Chassin (1999)]

- Mutations in Nef that flank this epitope, Thr71Lys and Ala83Gly, may account for an observed loss of CTL reactivity, with escape due to the introduction of proteasome processing reduction

Nef(73–82)	Nef(73–82)	QVPLRPMTYK	HIV-1 infection	human(A3)	[Durali (1998)]

- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env
- One of the patients was shown to react to this epitope: QVPLRPMTYK

Nef(73–82)	Nef(73–82 LAI)	QVPLRPMTYK	HIV-1 infection	human(A3)	[Goulder (1997e), Goulder (1997a)]

- Identical twin hemophiliac brothers were both infected with the same batch of factor VIII
- Both had a response to this epitope
- [Goulder (1997a)] is a review of immune escape that summarizes this study

Nef(73–82)	Nef(73–82)	QVPLRPMTYK	HIV-1 infection	human(A3)	[Lubaki (1997)]

- Eighty-two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response
- An A3+ subject had a strong response to this epitope, with 10/11 CTL clones being specific for this epitope, isolated at two time points, 1 year apart

Nef(73–82)	Nef(73–82)	QVPLRPMTYK	HIV-1 infection	human(A3)	[Samri (2000)]

- Epitope name: N1. The epitope was recognized by patients 252#0 and 252#4 in a study of the effects of therapy escape mutations on CTL recognition

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Nef(73–82)	Nef(73–82 SF2)	QVPLRRMTYK	HIV-1 infection	human(A3)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 3/7 group 1, 1/4 group 2, and 1/2 group 3

Nef(73–82)	Nef(73–82)	RLRDLLLIVTR	HIV-1 infection	human(A3)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant
- In two of the subjects, RLRDLLLIVTR was the dominant epitope

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Nef(73–82)	Nef( )	QVPLRPMTYK	HIV-1 infection	human(A3)	[Altfeld (2000)]

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual

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Nef(73–82)	Nef(73–82 LAI)	QVPLRPMTYK	HIV-1 infection	human(A3 supertype)	[Mollet (2000)]

- Epitope name: N1. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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Nef(73–82)	Nef(94–103)	QVPLRPMTYK	HIV-1 infection	human(A3 supertype)	[Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype), while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus

- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801)

Nef(73–82)	Nef(73–82 BRU)	QVPLRPMTYK	HIV-1 infection	human(A3, A11, B35)	[Culmann (1991)]

- Nef CTL clones from HIV+ donors

Nef(73–82)	Nef(73–82 LAI)	QVPLRPMTYK	HIV-1 infection	human(A3.1)	[Koenig (1995)]

- Alanine substitutions L76A, R77A, M79A, T80A significantly decreased immunogenicity of peptide
- Nef CTL clones (4N225) were infused into an HIV-1 infected volunteer to evaluate effects of infusion on viral load/patient health
- Infusion led to outburst of escape variants which resulted in higher viral load/accelerated disease progression

Nef(73–82)	Nef(73–82)	QVPLRPMTYK	HIV-1 infection	human(A3.1)	[Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- 1/11 of the A2+ individuals was A3, and responded to QVPLRPMTYK as well as two other A3.1 epitopes

Nef(73–82)	Nef(73–82)	QVPLRPMTYK	HIV-1 infection	human(B*0301)	[Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

Nef(73–82)	Nef(73–82 LAI)	QVPLRPMTYK		human(B27)	[Culmann(1998)]

- Optimal epitope mapped by peptide titration

Nef(73–82)	Nef(73–82 LAI)	SVPLRPMTYK	HIV-1 infection	human(B35 or C4)	[Buseyne (1993a)]

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed cytotoxic activity against at least one HIV protein was detected in 70% of infected children
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures
- Patient EM13, who had a CTL response to three epitopes in Nef, was infected via blood transfusion after birth and went from CDC stage P2A to P2E during the study

Nef(74–81)	Nef(74–82)	VPLRPMTY		human(A3)	[Carreno (1992)]
• Included in HLA-A3 binding peptide competition study					
Nef(74–81)	Nef(73–82 LAI)	VPLRPMTY	HIV-1 or HIV-2 infection	human(B*3501)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*3501 epitope					
Nef(74–81)	Nef(75–82)	VPLRPMTY	Peptide-HLA interaction	human(B*3501)	[Smith (1996)]
• Crystal structure of VPLRPMTY-class I B allele HLA-B*3501 complex					
Nef(74–81)	Nef( )	VPLRPMTY	HIV-1 infection	human(B*3501)	[Ostrowski (2000)]
• The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*					
• Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T-cell help in 9/10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T-cell help to a variable degree in most of patients					
• Those CTL that didn't respond to CD40LT could expand with IL-2 present, and IL-15 produced by dendritic cells also contributes					
• The T-helper epitope used for CD4+ T-cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKANSKFIGITE)					
Nef(74–81)	Nef(73–82 LAI)	VPLRPMTY	HIV-1 or HIV-2 infection	human(B35)	[Culmann (1991), McMichael & Walker(1994)]
• Review of HIV CTL epitopes – defined by B35 motif found within a larger peptide					
Nef(74–81)	Nef(73–82 LAI)	VPLRPMTY	HIV-1 or HIV-2 infection	human(B35)	[Rowland-Jones (1995)]
• VPLRPMTY also recognized by CTL from HIV-2 seropositives; epitope is conserved					
Nef(74–81)	Nef( )	VPLRPMTY	HIV-1 exposed seronegative	human(B35)	[Rowland-Jones (1998a)]
• A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating					
• The A and D subtype consensus are identical to the B clade epitope					
Nef(74–81)	Nef(75–82)	VPLRPMTY	*in vitro* stimulation	human(B35)	[Lalvani (1997)]
• A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers					
• This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors					
Nef(74–81)	Nef( )	VPLRPMTY	HIV-1 exposed seronegative	human(B35)	[Rowland-Jones (1998b)]
• HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection					
• Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world					
• Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes					

- This epitope is conserved among A, B, and D clade viruses

Nef(74–81)	Nef( )	VPLRPMTY		human(B35)	[Rowland-Jones (1999)]

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no δ32 deletion in CCR5
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive,
- HIV-2 version of this epitope is conserved: VPLRPMTY, and CTLs are cross-reactive – one of five B35 CTL epitopes that are cross-reactive, see also [Rowland-Jones (1995)]

Nef(74–81)	Nef(74–81)	VPLRPMTY	HIV-1 infection	human(B35)	[Oxenius (2000)]

- Epitope name: VPL. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- One of two HLA B35+ among the eight study subjects recognized this epitope
- Patient SC15 (HLA A1/68, B8/35, Bw4/6, Cw4/0704) was given acute and sustained therapy and recognized epitopes PPIPVGDIY and VPLRPMTY during 331 days of HAART treatment

Nef(74–81)	Nef(75–82)	VPLRPMTY	HIV-1 exposed seronegative, HIV-1 infection	human(B35)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Subject ML 857 shifted from an A*6802 DTVLEDINL and B35 H/NPDIVIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion

Nef(74–82)	Nef(73–82)	VPLRPMTYK	Peptide-HLA interaction	human(A11)	[Zhang (1993)]

- Exploration of A11 binding motif

Nef(75–82)	Nef(75–82 LAI)	PLRPMTYK	HIV-1 infection	human(A*1101)	[McMichael & Walker(1994), Brander & Goulder(2001)]

- Review of HIV CTL epitopes
- C. Brander notes that this is an A*1101 epitope

Nef(77–85)	Nef(77–85 LAI)	RPMTYKAAL	HIV-1 infection	human(B*0702)	[Bauer (1997)]

- Structural constraints on the Nef protein may prevent escape
- Noted in Brander 1999, this database, to be B*0702

Nef(77–85)	Nef(77–85 LAI)	RPMTYKAAL	HIV-1 infection	human(B*0702)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*0702 epitope

Nef(77–85)	Nef(75–83 IIIB)	RPMTYKAAL	HIV-1 infection	human(B7)	[Oxenius (2001b)]

- Study of tetramer staining of B7 around RPMTYKAAL gave quantitative results that were very different than functional measurements based on an ELISPOT assay
- Autologous clones were checked and 39/40 clones from two time points had the variant sequence RPMTYKGAL – tetramers based on RPMTYKGAL gave a more intense and uniform staining and bound with higher affinity to the RPMTYKGAL Vβ14 TCR

Nef(77–85)	Nef(77–85 SF2)	RPMTYKAAL	HIV-1 infection	human(B7)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 1/4 group 1, 0/3 group 2, and 1/1 group 3

Nef(77–85)	Nef(77–85)	RPMTYKAAL	HIV-1 infection	human(B7)	[Day (2001)]

- Both variants RPMTYKAA[V,L] served as epitopes
- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope

Nef(79–86)	Nef(81–89 HXB3)	MTYKAALDL	Vaccine	murine(HLA-A201 transgenic)	[Sandberg (2000)]

Vaccine: *Vector/type:* DNA, peptide *Strain:* HXB3 *HIV component:* Nef *Stimulatory Agents:* Freund's adjuvant

- Ten Nef 9-mer peptides were predicted to have a strong binding affinity with HLA-A*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly

- A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with either nef DNA under the control of a CMV promotor coated on, gold particles delivered to abdominal skin by gene gun
- MTYKAALDL bound weakly to HLA-A2, but the DNA nef vaccine elicited a good CTL response

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Nef(82–91) Nef(82–91 LAI) KAAVDLSHFL HIV-1 infection human(C*0802) [Nixon (1999)]

- A patient who made a mono-specific CTL response to this Nef specific epitope was given effective anti-retroviral therapy within 90 days of infection, reducing the antigenic stimulous
- Within 7 days of therapy, his CTLp frequency dropped from 60 to 4 per million PBMC, as his viremia dropped
- The patient went from having an activated effector population (detected by CTLp and clone specific RNA) to a non-activated quiescent population (detected by the CTL-clone specific DNA)

Nef(82–91) Nef(82–91 LAI) KAAVDLSHFL HIV-1 infection human(C*0802(Cw8)) [Brander & Goulder(2001)]

- C. Brander notes this is a C*0802(Cw8) epitope

Nef(82–91) Nef(82–91 SF2) KAAVDLSHFL HIV-1 infection human(Cw8) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-Cw8+ individuals that had a CTL response to this epitope broken down by group: 1/3 group 1, 0/0 group 2, and 0/1 group 3

Nef(82–91) Nef( ) KAAVDLSHFL HIV-1 infection human(Cw8) [Altfeld (2000)]

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual

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Nef(82–101) Nef(81–100 SF2) KAAVDLSHFLKEKGG-LEGLI HIV-1 infection human( ) [Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef
- Three of these 11 had CTL response to this peptide

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Nef(82–101)	Nef( )	KAAVDLSHFLKEKGG-LEGLI	HIV-1 infection	human( )	[Altfeld (2001a)]

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses is underestimated if accessory proteins are not included in the study
- Nef peptides PQVPLRRMTYKAAVDLSHFL, KAAVDLSHFLKEKGGLEGLI and EEEEVGFPVTPQVPLRPMTY were recognized and the first two share KAAVDLSHFL (a Cw8 epitope), the first and last share PQVPLRPMTY

Nef(83–91)	Nef(85–93 HXB3)	AALDLSHFL	Vaccine	murine(HLA-A201 transgenic)	[Sandberg (2000)]

Vaccine: *Vector/type:* DNA, peptide *Strain:* HXB3 *HIV component:* Nef *Stimulatory Agents:* Freund's adjuvant

- Ten Nef 9-mer peptides were predicted to have strong binding affinity for HLA-A*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly
- A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by gene gun
- AALDLSHFL was predicted to have a strong binding capacity for HLA-A2, and did, but it was the only one of the peptides recognized that was a strong binder, the other two recognized peptides were weak binders
- AALDLSHFL was also tested by subcutaneous injection of Nef peptides in Freund's adjuvant and gave a strong response to the peptide

Nef(83–92)	Nef(81–90 93TH253 CRF01)	GAFDLSFFLK	HIV-1 infection	human(A11)	[Sriwanthana (2001)]

- Epitope name: N83-92. This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand
- HLA-A11 is very common in this population, and was enriched among the HEPS sex workers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed
- This epitope was strongly reactive in HIV+ study subjects 053 and 184 who carried HLA A11

Nef(83–92)	Nef(81–90 93TH253 CRF01)	GAFDLSFFLK	HIV-1 infection	human(A11)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs; it was one of the six A11 epitopes that had been previously defined
- 4/8 tested FSWs recognized this epitope
- This epitope was only conserved in CRF01 and subtype C, and exact matches were uncommon

Nef(83–94)	Nef(83–94 BRU)	AAVDLSHFLKEK	HIV-1 infection	human(A11)	[Culmann (1991)]
• Epitope defined by boundaries of overlapping peptides that stimulate Nef CTL clones					
Nef(84–91)	Nef(84–91 LAI)	AVDLSHFL	HIV-1 infection	human(Bw62)	[Culmann-Penciolelli (1994)]
Nef(84–91)	Nef(84–91)	AVDLSHFL	HIV-1 infection	human(Bw62)	[Betts (2000)]
• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant					
• Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes					
• 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope					
Nef(84–92)	Nef(84–92 LAI)	AVDLSHFLK	HIV-1 infection	human(A*1101)	[Brander & Goulder(2001)]
• C. Brander notes this is an A*1101 epitope					
Nef(84–92)	Nef(84–92 LAI)	AVDLSHFLK	HIV-1 infection	human(A11)	[McMichael & Walker(1994)]
• Review of HIV CTL epitopes					
• C. Brander notes that this is an A*1101 epitope in the 1999 database					
Nef(84–92)	Nef(84–92)	AVDLSHFLK	HIV-1 infection	human(A11)	[Betts (2000)]
• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant					
• Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes					
• 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope					
Nef(84–92)	Nef(84–92 LAI)	AVDLSHFLK	HIV-1 infection	human(A11)	[Couillin (1994), Goulder (1997a)]
• Mutational variation in HIV epitopes in individuals with appropriate HLA types can result in evasion of CTL response					
• [Goulder (1997a)] is a review of immune escape that summarizes this study					
Nef(84–92)	Nef(84–92 LAI)	AVDLSHFLK	HIV-1 infection	human(A11)	[Couillin (1995)]
• Mutations found in this epitope in HLA-A11 positive and negative donors were characterized					
Nef(84–92)	Nef(84–92)	AVDLSHFLK	HIV-1 infection	human(A11)	[Oxenius (2000)]
• Epitope name: AVD. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable					
• Both of the 2/8 HLA-A11 study subjects recognized this CTL epitope					
• Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197					

	• Patient SC18(HLA A2/11, B8/44, Cw06/0701, DR3/7, DR52/53, DQ2) recognizes the epitopes ACQGVGGPGHK, QVPLRPMTYK, AVDLSHFLK, and one called QIY but not fully described – he had brief therapy upon seroconversion and has had low viral load during 600 days of follow up				
Nef(84–92)	Nef(82–90)	AVDLSHFLK	HIV-1 infection	human(A11)	[Ferrari (2000)]
	• One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles				
Nef(84–92)	Nef(84–92 SF2)	AVDLSHFLK	HIV-1 infection	human(A11)	[Altfeld (2001c)]
	• Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection • The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef • Previously described and newly-defined optimal epitopes were tested for CTL response • Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 2/2 group 3				
Nef(84–92)	Nef(84–92)	AVDLSHFLK	HIV-1 exposed seronegative, HIV-1 infection	human(A11)	[Kaul (2001a)]
	• ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers				
Nef(86–94)	Nef(86–94)	DLSHFLKEK	HIV-1 exposed seronegative, HIV-1 infection	human(A3)	[Kaul (2001a)]
	• ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers				
Nef(86–94)	Nef(84–92 LAI)	DLSHFLKEK	HIV-1 infection	human(A3.1)	[McMichael & Walker(1994)]
	• Review of HIV CTL epitopes				
Nef(86–100)	Nef(86–100 LAI)	DLSHFLKEKGGLEGL	HIV-1 infection	human(A2)	[Robertson (1993)]
	• Development of a retroviral vector (pNeoNef) to generate autologous targets				
Nef(86–100)	Nef(86–100 LAI)	DLSHFLKEKGGLEGL	HIV-1 infection	human(B35)	[Buseyne (1993b)]

Nef(86–100)	Nef(86–100 LAI)	DLSHFLKEKGGLEGL	HIV-1 infection	human(B35 or C4)	[Buseyne (1993a)]

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed cytotoxic activity against at least one HIV protein was detected in 70% of infected children
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures
- Patient EM13, who had a CTL response to three epitopes in Nef, was infected via blood transfusion after birth and went from CDC stage P2A to P2E during the study

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Nef(87–102)	Nef( )	FSHFLKEKGGLEGLIY		human( )	[Jubier-Maurin (1999)]

- 41 new HIV-1 strains describing envelope subtypes of HIV-1 A-H were genetically characterized in the nef region – 34 subtypes were classified in the same subtype in nef and env and 7 of the 41 strains were recombinants
- This region was defined as a CTL epitope region that is conserved among HIV-1 M group subtypes

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Nef(90–97)	Nef(92–99)	FLKEKGGL	HIV-1 infection	human(B8)	[Oxenius (2000)]

- Epitope name: FLK. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- Six of the 7/8 study subjects that were HLA B8 recognized this early dominant CTL epitope
- Patient SC2 (HLA A1, B7/8, Cw0701/0702, DR4/53, DQ7) had CTL responses against epitopes FLKEKGGL, GPKVKQWPL, and GEIYKRWII – FLKEKGGL tetramer staining steadily declined and at day 1340 the FLKEKGGL stained cells were no longer detected and the escape mutant FLKENGGI was found in 8/10 clones
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDLWIYHTQGYFPDWQNY, and GEIYKRWII and all responses declined during therapy initiated at day 390 but were restored when therapy became intermittent
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197
- Patient SC10(HLA A1/3, B8/35, DR1/8, DQ 4/5) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL and a response to GEIYKRWII through day 1088
- Patient SC12(HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKKKYKLK – GEIYKRWII and GGKKKYKLK responses were stimulated by a brief period off therapy
- Patient SC11(HLA A1, B8, Cw0201, DR3/11, DR52, DQ2/7) started therapy early, remained on therapy for 40 days, then reinitiated HAART at day 640, and had a CTL response to FLKEKGGL, GPKVKQWPL, and GEIYKRWII throughout and received a benefit from the early limited course therapy

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Nef(90–97)	Nef(89–97)	FLKEKGGL	HIV-1 infection	human( )	[Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes

- 1/11 of the A2+ individuals that responded to SLYNTVATL reacted with seven other epitopes including this epitope previously described as presented by B8

Nef(90–97) Nef( ) FLKEKGGL HIV-1 infection human(A3) [Ostrowski (2000)]

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T-cell help in 9/10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T-cell help to a variable degree in most of patients
- Those CTL that didn't respond to CD40LT could expand with IL-2 present, and IL-15 produced by dendritic cells also contributes
- The T-helper epitope used for CD4+ T-cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKANSKFIGITE)

Nef(90–97) Nef(89–97 LAI) FLKEKGGL HIV-1 infection human(B*0801) [Brander & Goulder(2001)]

- C. Brander notes this is a B*0801 epitope

Nef(90–97) Nef(89–97 LAI) FLKEKGGL HIV-1 infection human(B8) [Price (1997)]

- CTL escape variants appeared over time in HLA-B8 HIV-1+ individual, providing evidence of immune escape
- Most variants appear at position 5, an anchor residue
- FLKE(E,N or Q)GGL showed reduced binding efficiency and recognition
- Double mutants (FIKENGGL, FLEENGGL, and FLKGNGGL) completely escaped recognition
- [Goulder (1997a)] is a review of immune escape that summarizes this study in the context of CTL escape to fixation

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Nef(90–97) Nef(90–97 IIIB) FLKEKGGL HIV-1 infection human(B8) [Spiegel (1999)]

- Study examines the effect of highly active antiretroviral therapy (HAART) on HIV-1 plasma viral load, CTLp and CTLe frequencies in 8 infected children
- CTLp (precursors) were measured by stimulating in culture and assaying using 51Cr release, against vaccina expressed IIIB Env, Gag, Pol, Nef
- B7-FLKEKGGL tetramer complex was used for one of the children that was HLA-B7, and this infant showed a vigorous response (> 4% of CD8+ T-cells) at 9 months of age
- HIV-1 specific CTL responses initially increased in children with complete viral suppression, but then decreased, suggesting viral replication is needed to maintain CTL responses

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Nef(90–97) Nef( ) FLKEKGGL Vaccine human(B8) [Hanke (1998a), Hanke (1998b)]

Vaccine: *Vector/type:* vaccinia *HIV component:* polyepitope

- This epitope was shown to be processed and presented to appropriate CTL clones upon infection of human target cells with vaccinia virus Ankara (VVA) carrying 20 HIV-1 epitopes recognized by humans

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Nef(90–97) Nef(88–95) FLKEKGGL HIV-1 infection human(B8) [Goulder (1997g)]

- Natural variants for this epitope have been observed in several donors
- Substitutions Q5, N5, E5 that alter anchor position 5 are not well recognized
- Substitution I2 binds well to B8 and is recognized

Nef(90–97)	Nef(90–97)	FLKEKGGL	HIV-1 infection	human(B8)	[Dyer (1999)]

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load

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Nef(90–97)	Nef( )	FLKEKGGL	HIV-1 infection	human(B8)	[Goulder (2001b)]

- Epitope name: FL8. This peptide elicited a weak CTL response during acute HIV-1 infection in patient PI004
- Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond
- FL8 was recognized in an additional patient, AC29, in chronic infection

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Nef(90–97)	Nef(92–99)	FLKEKGGL	HIV-1 infection	human(B8)	[Oxenius (2001a)]

- Epitope name: FLK. Characterization of specific CTL phenotype patterns in response to variation of the virus load in response to antiviral therapy in 3 patients with chronic HIV-1 infection
- CTL activation in response to increasing viral load sequential, and co-segregated with apoptosis only during later stages of the response, suggesting antigen-specific cell-death is restricted to distinct CTL sub-populations

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Nef(90–97)	Nef( )	FLKEKGGL	HIV-1 infection	human(B8)	[Kostense (2001)]

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional
- In 15 of the patients, the proportion of IFNγ producing tetramer cells correlated with AIDS-free survival
- Stimulation with HLA-B8 p24 and Nef epitopes significantly increased Nef-specific T-cell numbers in 2 patients (748 and 1113)
- There were more functional IFN-γ producing Nef-specific T-cells within the T-cell population than there were active p24 Gag-specific T-cells
- No correlation between elevated numbers of Nef-specific CTL cells and plasma viral load was observed

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Nef(90–97)	Nef(88–95)	FLKEKGGL	HIV-1 infection	human(B8)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al*. as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

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Nef(90–97)	Nef(88–95 SF2)	FLKEKGGL	HIV-1 infection	human(B8)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response

- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 3/3 group 1, 1/3 group 2, and 1/2 group 3

Nef(90–97) Nef(89–97) FLKEKGGL HIV-1 infection human(B8) [Appay (2000)]

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV
- HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

Nef(90–97) Nef(90–97) FLKEKGGL HIV-1 infection human(B8) [Day (2001)]

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual
- The response to FLKEKGGL was the second highest response in magnitude compared to all the HLA class I A- and B-restricted epitopes tested in this individual

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Nef(90–97) Nef( ) FLKEKGGL HIV-1 infection human(B8) [Goulder (2000b)]

- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA])
- HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection

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Nef(92–100) ( ) KEKGGLEGL human(B*4001) [Brander & Goulder(2001)]

- C. Brander notes this is a B*4001,B60 epitope

Nef(92–100) Nef(91–99 BRU) KEKGGLEGL HIV-1 infection human(B*4002) [Mulligan (2001)]

- Epitope N10 from Patient 07118 with HLA genotypes A*0209, A*3201, B*4002, B*5301, Cw*0202, Cw*0401
- Epitope N10 Patient 07118 has 4 more optimal peptides P55, PIQKETWETW with HLA A*3201; G21 and G22, AEWDRVHPV with HLA B*4002; G31, QASQEVKNW with HLA B*5301;G43, TERQANFL with HLA B*4002

Nef(92–100) Nef(90–98 SF2) KEKGGLEGL HIV-1 infection human(B60) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B60+ individuals that had a CTL response to this epitope broken down by group: 2/2 group 1, 1/1 group 2, and 0/0 group 3

Nef(92–100)	Nef( )	KEKGGLEGL	HIV-1 infection	human(B60(B*4001)	[Altfeld (2000)]

- This epitope was the dominant B60 (encoded by B*4001) response in 6/8 HLA-B60 individuals, and recognized in all eight
- This epitope was also recognized two expressing HLA-B61 individuals (B61 is usually encoded by B*4002, but this study did not distinguish between B*4002, B*4003, B*4004, B*4006, and B*4008)
- ELISPOT was a rapid an effective method that was used to define five novel B60 epitopes
- HLA-B60 is present in 10-20% of the Caucasoid population and B60/B61 are very common in Asian populations

Nef(92–100)	Nef(92–100)	KEKGGLEGL	HIV-1 infection	human(B60/B61)	[Day (2001)]

- No immunodominant responses were detected to five B61-restricted epitopes tested in an HLA-B61 subject
- All five B60-restricted epitopes were reactive in an HLA-B60+ subject, and the B60-restricted responses together contributed over one-third of the total CTL response

Nef(92–112)	Nef( )	KEKGGLEGLIHSQRRQ-DILDL	HIV-1 infection	human( )	[Altfeld (2000)]

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined

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- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by a molecule other than B60 in an HLA-B60 individual
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined

Nef(93–106)	Nef(93–106 BRU)	EKGGLEGLIHSQRR	HIV-1 infection	human(A1, B8)	[Hadida (1992)]

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients

Nef(102–115)	Nef(102–115 LAI)	HSQRRQDILDLWIY	HIV-1 infection	human(B7)	[Goulder (1997e), Goulder (1997a)]

- Identical twin hemophiliac brothers were both infected with the same batch of factor VIII
- One had a strong response to this peptide, the other did not
- [Goulder (1997a)] is a review of immune escape that summarizes this study

Nef(102–121)	Nef(101–120 SF2)	HSQRRQDILDLQIYHT-QGYF	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef
- Two of these 11 had CTL response to this peptide
- The responding subjects were HLA-A2, A3, B8, B62 and HLA-A2, B21

Nef(103–127)	Nef(103–127 PV22)	SQRRQDILDLWIYHTQ-GYFPDWQNY	HIV-1 infection	human(B13)	[Jassoy (1993)]
• HIV-1 specific CTLs release γ-IFN, and α- and β-TNF					
Nef(103–127)	Nef(103–127)	SQRRQDILDLWIYHTQ-GYFPDWQNY	HIV-1 infection	human(B13)	[Oxenius (2000)]
• Epitope name: SQR. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable • The only study subject out of eight that was HLA B13+ recognized this epitope • Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDLWIYHTQGYFPDWQNY, and GEIYKRWII and all responses declined during therapy initiated at day 390 but were restored when therapy became intermittent				
Nef(105–114)	Nef(105–114 LAI)	RRQDILDLWI	HIV-1 infection	human(B*2705)	[Goulder (1997c)]
• Defined as optimal epitope from within reactive peptide HSQRRQDILDLWIYHTQGYF [Nef(102-121 LAI)] • HLA-B*2705 is associated with slow HIV disease progression • The HLA-B*2705 binding motif includes R at position 2, and L in the C-term position					
Nef(105–114)	Nef(105–114 LAI)	RRQDILDLWI	HIV-1 infection	human(B*2705)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*2705 epitope					
Nef(105–114)	Nef(105–114 SF2)	RRQDILDLWI	HIV-1 infection	human(B27)	[Altfeld (2001c)]
• Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection • The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef • Previously described and newly-defined optimal epitopes were tested for CTL response • Number of HLA-B27+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/1 group 3					
Nef(105–114)	Nef(105–114)	RRQDILDLWI	HIV-1 infection	human(B27)	[Day (2001)]
• B27-restricted CTL response was strongest to this epitope in one individual					
Nef(106–115)	( )	RQDILDLWIY		(B7)	[Brander & Goulder(2001), Goulder(1999)]

Nef(108–115)	Nef(107–114 BRU)	DILDLWIF	HIV-1 infection	human(Cw*0701, Cw*0706)	[Mulligan (2001)]
	• Epitope N11 from Patient 02112 with HLA genotypes A*3303, A*2601, B*5801, B*8201, Cw*0302, Cw*07(01, 06)				
	• Epitope N11 Patient 02112 has an other optimal peptide P61, ETKLGKAGY with HLA A*2601				
Nef(112–133)	Nef(111–132)	LWIYHTQGYFPDWQN-YTPGPGV	*in vitro* stimulation	human( )	[Lieberman (1995)]
	• HIV-specific CTL lines developed by *ex vivo* stimulation with peptide				
Nef(112–133)	Nef(111–132 SF2)	LWIYHTQGYFPDWQN-YTPGPGV	HIV-1 infection	human( )	[Lieberman (1997a)]
	• Of 25 patients, most had CTL specific for more than one HIV-1 protein				
	• Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef				
	• Four of these 11 had CTL response to this peptide				
	• The responding subjects were HLA-A2, B21; HLA-A1, A3, B7, B15; HLA-A2, A26, B7, B38				
Nef(112–133)	Nef(111–132 SF2)	LWIYHTQGYFPDWQN-YTPGPGV	HIV-1 infection	human( )	[Lieberman (1997b)]
	• CTL expanded *ex vivo* were later infused into HIV-1 infected patients				
Nef(113–125)	Nef(113–125 BRU)	WIYHTQGYFPDWQ	HIV-1 infection	human(B17)	[Culmann (1989)]
	• Nef CTL clones from HIV+ donors				
Nef(113–126)	Nef( )	VYHTQGYFPDWQNY	HIV-1 infection	human( )	[Jubier-Maurin (1999)]
Nef(113–128)	Nef(113–128 BRU)	WIYHTQGYFPDWQNY-T	HIV-1 infection	human(A1)	[Hadida (1992)]
	• HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients				
Nef(113–128)	Nef(113–128 LAI)	WIYHTQGYFPDWQNY-T	HIV-1 infection	human(A1)	[Mollet (2000)]
	• Epitope name: N2. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses				
	• In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished				
	• Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change				
Nef(115–125)	Nef(115–125 BRU)	YHTQGYFPDWQ	HIV-1 infection	human(B17)	[Culmann (1991)]
	• Nef CTL clones from HIV+ donors				

Nef(116–125)	Nef(116–125 BRU)	HTQGYFPDWQ	HIV-1 infection	human(B*5701)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*5701 epitope					
Nef(116–125)	Nef(116–125)	HTQGYFPDWQ	HIV-1 infection	human(B57)	[Betts (2000)]
• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant • Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes • One of the individuals that was HLA-A2+, but otherwise of unknown HLA type, and reacted with seven epitopes including this one					
Nef(116–125)	Nef(116–125 BRU)	HTQGYFPDWQ	HIV-1 infection	human(B57)	[Culmann (1991)]
• Nef CTL clones from HIV+ donors, optimal peptide mapped					
Nef(116–125)	Nef(116–125)	HTQGYFPDWQ	HIV-1 infection	human(B57)	[Oxenius (2000)]
• Epitope name: HTQ. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable • None of the 8 study subjects recognized this epitope but none were HLA B57+					
Nef(117–127)	Nef(117–127)	TQGYFPDWQNY	HIV-1 infection	human( )	[Betts (2000)]
• Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant • Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes • 1/11 of the A2+ individuals was HLA A*0205/A*0208, A30, B27, B44 but responded to HLA Bw62 epitope TQGYFPDWQNY, and one of the other individuals that was A2+, but otherwise of unknown HLA type, reacted with seven epitopes including this one					
Nef(117–127)	Nef(117–127 LAI)	TQGYFPDWQNY	HIV-1 infection	human(B*1501)	[Brander & Goulder(2001)]
• C. Brander notes this is a B*1501 epitope					
Nef(117–127)	Nef(117–127)	TQGYFPDWQNY	HIV-1 infection	human(B62)	[Day (2001)]
• No immunodominant responses were detected to four B62-restricted epitopes tested					
Nef(117–127)	Nef(117–127 LAI)	TQGYFPDWQNY	HIV-1 infection	human(Bw62)	[Culmann(1998)]
• Optimal peptide defined by titration					
Nef(117–128)	Nef(117–128 BRU)	TQGYFPDWQNYT	HIV-1 infection	human(B17, B37)	[Culmann (1991)]
• Nef CTL clones from HIV+ donors					
Nef(117–147)	Nef(117–147 LAI)	TQGYFPDWQNYTPGP-GVRYPLTFGWCYKLVP	Vaccine	human( )	[Gahery-Segard (2000)]

Vaccine: *Vector/type:* lipopeptide *HIV component:* six peptides

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 1/10 reacted to this Nef peptide
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual
- 10/12 tested had an IgG response to this peptide

Nef(118–127)	Nef(118–127 LAI)	QGYFPDWQNY		human(Bw62)	[McMichael & Walker(1994)]

- Review of HIV CTL epitopes

Nef(120–128)	Nef(120–128)	YFPDWQNYT	HIV-1 infection	human( )	[Betts (2000)]

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant
- Ninety-five optimally-defined peptides from this database were used to screen for γ interferon responses to other epitopes
- 1/11 of the A2+ individuals was HLA A*0205/A*0208, A30, B27, B44 but responded to HLA B37 epitope IYKRWIILGL, and one of the other individuals that was A2+, but otherwise of unknown HLA type, reacted with seven epitopes including this one

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Nef(120–128)	Nef(118–126 SF2)	YFPDWQNYT	HIV-1 infection	human(A1)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A1+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/2 group 2, and 1/2 group 3

Nef(120–128)	Nef(120–128 LAI)	YFPDWQNYT	HIV-1 infection	human(B*3701)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*3701 and B*5701 epitope

Nef(120–128)	Nef(120–128 LAI)	YFPDWQNYT	HIV-1 infection	human(B*5701)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*5701 epitope
- Subtype of B57 not determined

Nef(120–128)	Nef(120–128 IIIB)	FFPDWKNYT	HIV-1 infection	human(B15)	[Wilson (1999a)]

- This study describes maternal CTL responses in the context of mother-to-infant transmission
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants
- LFPDWKNYT is an escape mutant

Nef(120–128)	Nef(120–128 LAI)	YFPDWQNYT	HIV-1 infection	human(B37,B57)	[Culmann(1998)]
• Nef CTL clones from HIV+ donors – optimum peptide mapped by titration					
Nef(120–144)	Nef(120–144 SF2)	YFPDWQNYTPGPGIR-YPLTFGWCYK	HIV-1 infection	human(A24)	[Jassoy (1992)]
• Epitope recognized by CTL clone derived from CSF					
Nef(122–141)	Nef(121–140 SF2)	PDWQNYTPGPGVRYP-LTFGW	HIV-1 infection	human( )	[Lieberman (1997a)]
• Of 25 patients, most had CTL specific for more than one HIV-1 protein • Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef • Three of these 11 had CTL response to this peptide • The responding subjects were HLA-A2, B21; HLA-A3, A24, B7, B38					
Nef(123–137)	Nef(123–137 IIIB)	QWQNYTPGPGVRYPL	HIV-1 infection	human( )	[Wilson (1996)]
• Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study • FFPDYTPGPGTRFPL and FFPDYKPGPGTRFPL, naturally occurring variants, were found in the mother and are not recognized • LFPDYKPGPGTRFPL and FFPDYKPGPGTRFPL, naturally occurring variants, were found in the infant and are not recognized					
Nef(126–138)	Nef(126–138 BRU)	NYTPGPGVRYPLT	HIV-1 infection	human(B7)	[Culmann (1991)]
• Nef CTL clones from HIV+ donors					
Nef(128–135)	Nef(128–135 LAI)	TPGPGVRY	*in vitro* stimulation	human(B*0702)	[Lucchiari-Hartz (2000)]
• Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152 • All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments • Both TPGPGVRYPL and TPGPGVRY are naturally processed ligands that can be eluted from HLA-B7 molecules, both are recognized by the same CTL, and both peptides seem to be the direct product of a proteasomal digest • The peptide TPGPGVRY is present in a high copy number, TPGPGVRYPL at a more moderate level, possibly due to a major cleavage site between the Y and P					
Nef(128–137)	Nef( )	TPGPGIRYPL	HIV-1 infection	human( )	[Kaul (2001b)]
• This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative • The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire • This epitope was recognized by 1/22 HEPS control sex workers, ML851					

Nef(128–137)	Nef(128–137 LAI)	TPGPGVRYPL	HIV-1 infection	human(B*0702)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*0702 epitope

Nef(128–137)	Nef(128–137 LAI)	TPGPGVRYPL	*in vitro* stimulation	human(B*0702)	[Lucchiari-Hartz (2000)]

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments
- Both TPGPGVRYPL and TPGPGVRY are naturally processed ligands that can be eluted from HLA-B7 molecules, both are recognized by the same CTL, and both peptides seem to be the direct product of a proteasomal digest
- The peptide TPGPGVRY is present in a high copy number, TPGPGVRYPL at a more moderate level, possibly due to a major cleavage site between the Y and P

Nef(128–137)	Nef(128–137 LAI)	TPGPGVRYPL		human(B*4201)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*4201 epitope

Nef(128–137)	( )	TPGPGVRYPL	HIV-1 infection	human(B7)	[Wilson (2000)]

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T-cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and was appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK
- The subject with A*0201 had a moderately strong response to SLYNTVATL
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL

Nef(128–137)	Nef(128–137 LAI)	TPGPGVRYPL	HIV-1 infection	human(B7)	[Haas (1996), Haas (1997)]

- There was a high degree of variation in three CTL epitopes in Nef in four slow and non-progressors, and variant specific CTLs arose over time to eliminate variants, indicating immune selection
- The epitope position was taken from [Haas (1997)]

Nef(128–137)	Nef( )	TPGPGVRYPL	HIV-1-exposed seronegative	human(B7)	[Rowland-Jones (1998a)]

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating

- The D subtype consensus is identical to the B clade epitope
- The A subtype consensus is TPGPGIRYPL

Nef(128–137)	Nef( )	TPGPGVRYPL	HIV-1-exposed seronegative	human(B7)	[Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among B and D clade viruses
- The clade A version of the epitope: TPGPGIRYPL

Nef(128–137)	Nef(128–137)	TPGPGVRYPL	*in vitro* stimulation	human(B7)	[Wilson (1999b)]

- Dendritic cells are the most potent for priming T-cell responses – DCs can stimulate autologous CTL responses from T-cells cultured from HIV negative donors
- Th1-biasing cytokines IL-12 or IFNα enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within
- CTL from a B7 donor displayed no reactivity to this epitope, although it had been immunodominant in another study [Haas (1996)]

Nef(128–137)	Nef(128–137 SF2)	TPGPGVRYPL	HIV-1 infection	human(B7)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3

Nef(128–137)	Nef(128–137)	TPGPGVRYPL	HIV-1-exposed seronegative, HIV-1 infection	human(B7)	[Kaul (2001a)]

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure

- Among HLA-B7 women, 4/5 HEPS and 5/6 HIV-1-infected women recognized this epitope
- The dominant response to this HLA allele was to this epitope in 3 of the 4/5 HEPS cases and in 2 of the 5/6 HIV-1-infected women
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV

Nef(128–137) Nef(128–137) TPGPGVRYPL HIV-1 infection human(B7) [Appay (2000)]

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T-cells specific for HIV and CMV
- HIV-specific CD8+ T-cells expressed lower levels of perforin than CMV-specific CD8+ T-cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T-cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

Nef(128–137) Nef(128–137) TPGPGVRYPL HIV-1 infection human(B7) [Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope

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Nef(128–137) Nef( ) TPGPGVRYPL HIV-1-exposed seronegative human(B7(*8101)) [Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- Clade A version of the epitope: TPGPGIRYPL, clade D version: TPGPGIRYPL

Nef(128–137) Nef(128–137 clade B) TPGPGVRYPL HIV-1-exposed seronegative human(B7,B*8101) [Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells
- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women

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Nef(130–143)	Nef(130–143 LAI)	GPGVRYPLTFGWCY	HIV-1 infection	human(B*57)	[Goulder (1996b)]

- CTL response to this epitope observed in 4 long-term survivors
- Peptide defined on the basis of B*5801 binding motif, yet not cross-restricted except at high concentrations

Nef(130–143)	Nef(121–141)	GPGVRYPLTFGWCY	HIV-1 infection	human(B57)	[Ferrari (2000)]

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles

Nef(131–143)	Nef( )	GIRYPLTFGWCFK		human( )	[Jubier-Maurin (1999)]

- 41 new HIV-1 strains describing envelope subtypes of HIV-1 A-H were genetically characterized in the nef region – 34 subtypes were classified in the same subtype in nef and env and 7 of the 41 strains were recombinants
- This region was defined as a CTL epitope region that is conserved among HIV-1 M group subtypes

Nef(132–147)	Nef(132–147 BRU)	GVRYPLTFGWCYKLVP	HIV-1 infection	human(A1, B8)	[Hadida (1992)]

- HIV-1 specific CTLs detected in lymphoid organs

Nef(132–147)	Nef(132–147 BRU)	GVRYPLTFGWCYKLVP	HIV-1 infection	human(B18)	[Culmann (1991)]

- Nef CTL clones from HIV+ donors

Nef(132–147)	Nef(132–147)	GVRYPLTFGWCYKLVP	Vaccine	murine(H-2^d)	[Billaut-Mulot (2001)]

Vaccine: *Vector/type:* DNA with DNA boost, DNA with recombinant protein boost *Strain:* LAI *HIV component:* Gag, Tat, Nef *Stimulatory Agents:* IL-18

- DNA vaccinated BALB/c mice primed and boosted with the multiepitopic vaccine with IL-18 showed lymphoproliferative responses 7 weeks post immunization
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime/DNA boost was more effective than DNA prime protein boost
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine induced HIV-1 specific Th1 cytokines (IL-2 and IFN-γ)
- Co-administration of IL-18 increased T-cell responses but decreased anti-HIV antibody levels

Nef(133–148)	Nef(133–148 LAI)	VRYPLTFGWCYKLVPV		human(B57)	[Brander & Walker(1996)]

- P. Goulder, pers. comm.

Nef(134–141)	Nef(138–147 LAI)	RYPLTFGW	HIV-1 infection	human(A*2402)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*2402 epitope

Nef(134–141)	Nef(138–147 SF2)	RYPLTFGW	HIV-1 infection	human(A24)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection

- The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A24+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 2/3 group 2, and 0/0 group 3

Nef(134–141)	Nef(134–141 LAI)	RYPLTFGW		human(B27)	[Culmann(1998)]

- Optimal peptide defined by titration

Nef(134–143)	Nef(138–147 SF2)	RYPLTFGWCF	HIV-1 infection	human(A*2402)	[Ikeda-Moore (1997)]

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402
- This peptide induced CTL in 3/4 HIV-1+ people tested
- RYPLTFGWCF bound to A*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained

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Nef(134–144)	Nef(134–144 LAI)	RYPLTFGWCYK	HIV-1 infection	human(B18)	[Couillin (1994), Goulder (1997a)]

- Mutational variation in HIV epitopes in individuals with appropriate HLA types can result in evasion of CTL response
- [Goulder (1997a)] is a review of immune escape that summarizes this study

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Nef(134–144)	Nef(134–144)	RYPLTFGWCYK	HIV-1 infection	human(B18)	[Oxenius (2000)]

- Epitope name: RYP. Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable
- None of the 8 study subjects recognized this epitope but none were HLA B18+

Nef(135–143)	Nef(135–143 LAI)	YPLTFGWCY	*in vitro* stimulation	human(B*0702)	[Lucchiari-Hartz (2000)]

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments
- YPLTFGWCY is the naturally processed ligand for B7, and this epitope is the only one of the five that may require trimming at the N-termini
- YPLTFGWCY is present in low copy number in the cell, possibly due to a predominant proteasomal cleavage site between Y and P

Nef(135–143)	Nef(135–143 LAI)	YPLTFGWCY	HIV-1-exposed seronegative	human(B*1801)	[Brander & Goulder(2001)]

- C. Brander notes this is a B*1801 epitope

Nef(135–143)	Nef(134–142 BRU)	YPLTFGWCY	HIV-1 infection	human(B*5301)	[Mulligan (2001)]

- Epitope N14 from Patient 07107 with HLA genotypes A*3002, A*3201, B*4501, B*5301, Cw*0401, Cw*1202

Nef(135–143)	Nef( )	YPLTFGWCF	HIV-1-exposed seronegative	human(B18)	[Kaul (2000)]

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 γ-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses
- Low risk individuals did not have such CD8+ cells
- CD8+ T-cell epitopes DTVLEDINL (3 individuals), SLYNVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women

Nef(135–143)	Nef(135–143 LAI)	YPLTFGWCY	HIV-1-exposed seronegative	human(B18)	[Culmann (1991), Culmann-Penciolelli (1994)]

- Nef CTL clones from HIV+ donors

Nef(135–143)	Nef(135–143 SF2)	YPLTFGWCY	HIV-1 infection	human(B18)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-B18+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 1/2 group 2, and 0/0 group 3

Nef(135–143)	Nef(135–143)	YPLTFGWCY	HIV-1-exposed seronegative, HIV-1 infection	human(B18,B49)	[Kaul (2001a)]

- Variants YPLTFGWC[Y/F] are specific for the B/D clades
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1-infected women
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure
- Among HLA-B18 women, 1/4 HEPS and 8/9 HIV-1-infected women recognized this epitope, likelihood ratio 5.3, p value 0.04, and HEPS women tended to respond to FRDYVDRF[Y/F]K, while infected women tended to respond to YPLTFGWC[Y/F]
- The dominant response to this HLA allele was to this epitope for the one reactive HEPS case and in all 8/9 HIV-1-infected women

- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort

Nef(135–143)	Nef(139–147 SF2) • Binds HLA-B*3501	YPLTFGWCF	HIV-1 infection	human(B35)	[Shiga (1996)]
Nef(135–143)	Nef( )	YPLTFGWCY	HIV-1-exposed seronegative	human(B49)	[Rowland-Jones (1998a)]

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating
- The A subtype consensus is identical to the B clade epitope
- The D subtype consensus is YPLTFGWCf

Nef(135–143)	Nef( )	YLPTFGWCY	HIV-1-exposed seronegative	human(B49)	[Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- This epitope is conserved among A and B clade viruses
- The clade D version of the epitope, YPLTFGWCF, was preferentially recognized by CTL

Nef(135–143)	( )	YPLTFGWCY	HIV-1 infection	human(B49)	[Kaul (2001b)]

- This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative
- The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire
- This epitope (YPLTFGWCY/F) was recognized in 1/22 HEPS sex worker controls (ML1668)

Nef(136–145)	Nef(136–145)	PLTFGWCYKL	*in vitro* stimulation	human(A2)	[Wilson (1999b)]

- Dendritic cells are the most potent for priming T-cell responses – DCs can stimulate autologous CTL responses from T-cells cultured from HIV negative donors
- Th1-biasing cytokines IL-12 or IFNα enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within
- B7 and A2 Nef epitopes were studied and the relative binding affinity of A2 epitopes for A2 was: PLTFGWCYKL greater than VLEWRFDSRL which was much greater than AFHHVAREL

Nef(136–145)	Nef(136–145 LAI)	PLTFGWCYKL		human(A*0201)	[Brander & Goulder(2001)]

- C. Brander notes this is an A*0201 epitope

Nef(136–145)	Nef(136–145 LAI)	PLTFGWCYKL	*in vitro* stimulation	human(A*0201)	[Lucchiari-Hartz (2000)]

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments
- The CTL that recognized PLTFGWCYKL also recognized PLTFGWCYKLV, and both forms of the epitope are naturally processed and both seem to be the direct product of a proteasomal digest, although in low copy number

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Nef(136–145)	Nef(136–145)	PLTFGWCFKL	HIV-1 infection	human(A2)	[Durali (1998)]

- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env
- Patient B18 had the greatest breadth and diversity of response, and recognized Gag SLYNTVATL and Nef PLTFGWCFKL

Nef(136–145)	Nef(157–166)	PLTFGWCFKL	Vaccine	human(A2)	[Woodberry (1999)]

Vaccine: *Vector/type:* DNA prime with vaccinia boost *HIV component:* polyepitope

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested
- PLTFGWCFKL was recognized by 1 of the HLA-A2 patients

Nef(136–145)	Nef(135–144 93TH253 CRF01)	PLTFGWCYKL	HIV-1 infection	human(A2)	[Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested
- 0/4 tested FSWs recognized the E clade version of this epitope PLCFGWCFKL, which differs from the previously defined B clade version by two amino acids, PLTFGWCYKL
- This epitope was only conserved in CRF01 (subtype E) and subtype B

Nef(136–145) Nef(136–145) PLTFGWCYKL HIV-1 infection human(A2) [Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person

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Nef(136–145) Nef(158–166) LTFGWCFKL HIV-1 infection human(A2 supertype) [Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype), while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)

Nef(136–146) Nef(136–146 LAI) PLTFGWCYKLV *in vitro* stimulation human(A*0201) [Lucchiari-Hartz (2000)]

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments
- The CTL that recognized PLTFGWCYKL also recognized PLTFGWCYKLV, and both forms of the epitope are naturally processed and both seem to be the direct product of a proteasomal digest, although in low copy number

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Nef(136–146) Nef(158–167) LTFGWCFKLV HIV-1 infection human(A2 supertype) [Propato (2001)]

- Long-term non-progressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested (18 for the A2 supertype, 16 for the A3 supertype), while the effector cells of long-term non-progressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus
- This epitope can bind five HLA-A2 supertype alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)
- Tetramer staining with A2, β2-microglobulin, and either SLYNTVATL, KLVGKLNWA, or LTFGWCFKL revealed that tetramers detected more HIV-specific cells in LTNP than in progressors, activated effector cells were the minority population, and ELISPOT correlated better with the effector cell subpopulation than the total tetramer stained population

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Nef(137–146)	Nef( )	LTFGWCFKLV	HIV-1 infection	human(A2)	[Altfeld (2001d)]

- Epitope name: Nef-221a. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- 1/22 individuals with chronic HIV-1 infection recognized this epitope in ELISPOT
- 2/12 acutely infected individuals recognized this epitope
- LTFGWCFKLV binds to five HLA-A2 supertype alleles:A*0203, A*0201 (highest affinity), A*0206, A*6802 and A*0202

Nef(162–181)	Nef(161–180)	TSLLHPVSLHGMDDP-EREVL	*in vitro* stimulation	human( )	[Lieberman (1995)]

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide

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Nef(162–181)	Nef(161–180 SF2)	TSLLHPVSLHGMDDP-EREVL	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef
- One of these 11 had CTL response to this peptide

Nef(162–181)	Nef(101–120 SF2)	TSLLHPVSLHGMDDP-EREVL	HIV-1 infection	human( )	[Lieberman (1997b)]

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients

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Nef(162–181)	Nef(161–180 SF2)	TSLLHPVSLHGMDDP-EREVL	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef
- One of these 11 had CTL response to this peptide

Nef(166–177)	Nef(160–179 SF2)	HPVSLHGMDDPE	HIV-1 infection	human(B35)	[Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response

- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 0/1 group 3

Nef(172–191) Nef(171–190 SF2) GMDDPEREVLEWRFD-SRLAF HIV-1 infection human( ) [Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef
- One of these 11 had CTL response to this peptide
- The responding subject was HLA-A2, B21

Nef(175–184) Nef(175–184) DPEKEVLQWK HIV-1 infection human(B7) [Jin (2000b)]

- This a B7 epitope, a subdominant CTL response, was defined by an un-conventional approach used to predict epitopes in an HLA B7+ long-term non-progressor
- Three additional sub-dominant HLA B7 epitopes were defined using EpiMatrix, a non-anchor based strategy for defining potential epitopes, which highlighted 2078 possible epitopes in the autologous HIV-1 derived from the study subject, followed by B7 anchor residue prediction which narrowed the set to 55 peptides, three of which could serve as functional CTL epitopes

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Nef(179–187) Nef( ) AFHHVAREL HIV-1 infection human(A*0201) [Altfeld (2001d)]

- Epitope name: Nef AL9. HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested
- Three additional previously described HLA-A2 epitopes were added to the set of 20, including Nef AL9, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acutely infected individuals recognized at least 1 (median of 1 and maximum of 2)
- RT VL9 was not recognized by any of the 22 HLA-A2 patients with chronic HIV-1 infection or the 13 HLA-A2 patients with acute HIV-1 infection included in this study

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Nef(180–189) Nef(180–189 LAI) VLEWRFDSRL HIV-1 infection human(A*0201) [Haas (1996), Haas (1997)]

- There was a high degree of variation in three CTL epitopes in Nef in four slow and non-progressors, and variant specific CTLs arose over time to eliminate variants, indicating immune selection
- Noted in Brander *et al*., 1999 this database, to be A*0201

Nef(180–189) Nef(180–189 LAI) VLEWRFDSRL human(A*0201) [Brander & Goulder(2001)]

- C. Brander notes this is an A*0201 epitope

Nef(180–189) Nef(180–189) VLEWRFDSRL *in vitro* stimulation human(A2) [Wilson (1999b)]

- Dendritic cells are the most potent for priming T-cell responses – DCs can stimulate autologous CTL responses from T-cells cultured from HIV negative donors

- Th1-biasing cytokines IL-12 or IFNα enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within
- B7 and A2 Nef epitopes were studied and the relative binding affinity of A2 epitopes for A2 was: PLTFGWCYKL greater than VLEWRFDSRL which was much greater than AFHHVAREL

Nef(180–189) Nef(180–189) VLEWRFDSRL Vaccine human(A2) [Woodberry (1999)]

Vaccine: *Vector/type:* DNA prime with vaccinia boost *HIV component:* polyepitope

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested
- VLEWRFDSRL was recognized by 2 of the HLA-A2 patients

Nef(180–189) Nef(180–189 LAI) VLEWRFDSRL HIV-1 infection human(A2) [Mollet (2000)]

- Epitope name: N3. A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNγ production to measure responses
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change

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Nef(180–189) Nef(179–188 93TH253 CRF01) VLEWRFDSRL HIV-1 infection human(A2) [Bond (2001)]

- HLA-A11 CRF01 (called subtype E in Bond *et al*.) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive so the study concentrated on A11 epitopes, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested
- 0/4 tested FSWs recognized the E clade version of this epitope VLIWKFDSAL, which differs from the previously defined B clade version by three amino acids, VLEWRFDSRL
- This epitope was only conserved in CRF01 (subtype E), and identities were rare

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Nef(180–189)	Nef(180–189)	VLEWRFDSRL	HIV-1 infection	human(A2)	[Day (2001)]

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who co-expressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- Two to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person

Nef(182–198)	Nef(182–198 BRU)	EWRFDSRLAFHHVAR-EL	HIV-1 infection	human(A1, B8)	[Hadida (1992)]

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients

Nef(182–198)	Nef(182–198 LAI)	EWRFDSRLAFHHVAR-EL	HIV-1 infection	human(A2, A25(10))	[Hadida (1995)]

- The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions

Nef(182–198)	Nef(182–198 BRU)	EWRFDSRLAFHHVAR-EL	HIV-1 infection	human(A25)	[Cheynier (1992)]

- CTL isolated in children born to HIV-1 positive mothers

Nef(182–198)	Nef(182–198 LAI)	EWRFDSRLAFHHVAR-EL	HIV-1 infection	human(B35)	[Hadida (1995)]

- The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions

Nef(182–198)	Nef(182–198 LAI)	EWRFDSRLAFHHVAR-EL	Vaccine	murine(H-2^d)	[Van der Ryst (1998)]

Vaccine: *Vector/type:* Mengo virus, vaccinia *Strain:* LAI *HIV component:* Nef

- Macaca mulatta did not have a detectable response to Rec Mengo virus-HIV-1 Nef 65-206 vaccine
- BALB/c mice had a weak response to this epitope in the Mengo virus construct – in contrast, HIV-1 Nef induces a strong CTL response in mice when presented in a vaccinia background

Nef(182–201)	Nef(191–205 SF2)	EWRFDSRLAFHHVAR-ELHPE	HIV-1 infection	human( )	[Lieberman (1997a)]

- Of 25 patients, most had CTL specific for more than one HIV-1 protein
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef
- One of these 11 had CTL response to this peptide
- The responding subject was HLA-A2, B21

Nef(182–205)	Nef(182–205 LAI)	EWRFDSRLAFHHVAR-ELHPEYFKN	Vaccine	human( )	[Gahery-Segard (2000)]

Vaccine: *Vector/type:* lipopeptide *HIV component:* six peptides

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial
- A CD4+ T-cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 4/10 reacted to this Nef peptide
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual
- None of the 12 tested had an IgG response to this peptide

Nef(183–191)	Nef(182–190 BRU)	WRFDSRLAF	HIV-1 infection	human(B*1503)	[Mulligan (2001)]
• Epitope N18 from Patient 11113 with HLA genotypes A*2904, A*3002, B*1503, B*5802, Cw*0202, Cw*0602					
Nef(186–193)	Nef(186–193 LAI)	DSRLAFHH	HIV-1 infection	human(B35)	[Hadida (1995)]
• The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions					
Nef(186–194)	Nef(186–194)	DSRLAFHHM	HIV-1-exposed seronegative, HIV-1 infection	human(A24)	[Kaul (2001a)]
• ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers					
Nef(186–194)	Nef(186–194 BRU)	DSRLAFHHV		human(B51)	[Connan (1994)]
• Resulted in the assembly of HLA-B51					
Nef(188–196)	Nef(188–196 LAI)	RLAFHHVAR	HIV-1 infection	human(B52)	[Hadida (1995)]
• The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions					
Nef(188–201)	Nef(188–201 LAI)	RLAFHHVARELHPE	HIV-1 infection	human(B35 or C4)	[Buseyne (1993a)]
• Vertical transmission of HIV ranges from 13% to 39% • Primary assays showed cytotoxic activity against at least one HIV protein was detected in 70% of infected children • Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures • Patient EM13, who had a CTL response to three epitopes in Nef, was infected via blood transfusion after birth and went from CDC stage P2A to P2E during the study					
Nef(190–198)	( )	ALKHRAYEL	HIV-1 infection	human( )	[Kaul (2001b)]
• This study examines CTL responses in HIV-exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative • The epidemiological factor associated with seroconversion was stopping sex work and HIV-specific CTL activity declines when HEPS sex workers stop working for a period or retire • This epitope was in 1/22 HEPS controls, ML1749					

Nef(190–198) Nef(190–198 LAI) AFHHVAREL HIV-1-exposed seronegative human(A2) [Rowland-Jones (1998a)]

- CTL recognition reported in the context of HLA-B52 and A2.1, A2.2 and A2.4
- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating
- The A subtype consensus is ALKHRAYEL
- The D subtype consensus is AfEHKAREm
- [Hunziker1998] maintains that HLA-A2 does not present this epitope contrary to an earlier report [Hadida (1995)], (also see [Brander (1998)]) – despite the position of Hunziker *et al.*, Rowland-Jones and colleagues are confident that this epitope in its A clade form is presented by HLA-A*0201 and A*0202, and it is one of the most common responses seen in both seropositive and exposed-uninfected donors from Nairobi (Rupert Kaul, Pers. Comm.)

Nef(190–198) Nef(190–198) AFHHVAREL *in vitro* stimulation human(A2) [Wilson (1999b)]

- Dendritic cells are the most potent for priming T-cell responses – DCs can stimulate autologous CTL responses from T-cells cultured from HIV negative donors
- Th1-biasing cytokines IL-12 or IFNα enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within
- B7 and A2 Nef epitopes were studied and the relative binding affinity of A2 epitopes for A2 was: PLTFGWCYKL greater than VLEWRFDSRL which was much greater than AFHHVAREL

Nef(190–198) Nef(190–198) AFHHVAREL Vaccine human(A2) [Woodberry (1999)]

Vaccine: *Vector/type:* vaccinia *HIV component:* polyepitope

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested
- AFHHVAREL was recognized by 2 of the patients

Nef(190–198) Nef(190–198 SF2) AFHHVAREL HIV-1 infection human(A2) [Altfeld (2001c)]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection

- The breadth and specificity of the response were determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Previously described and newly-defined optimal epitopes were tested for CTL response
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 0/10 group 1, 1/6 group 2, and 0/4 group 3

Nef(190–198)	Nef(190–198)	ALKHRAYEL	HIV-1-exposed seronegative, HIV-1 infection	human(A2)	[Kaul (2001a)]

- Variants ALKHRAYEL and AFHHVAREL are A/B clade specific
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers

Nef(190–198)	Nef( )	AFHHVAREL	HIV-1-exposed seronegative	human(A2, A*0202, A*0201)	[Rowland-Jones (1998b)]

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes
- Clade A version of the epitope: ALKHRAYEL, clade D epitope: AFEHKAREM
- This epitope was recognized by two different exposed and uninfected prostitutes

Nef(190–198)	Nef(190–198 LAI)	AFHHVAREK	HIV-1 infection	human(A3)	[Hadida (1995)]

- Naturally-occurring L to K anchor substitution abrogates A2 binding, but permits HLA-A3 binding

Nef(192–206)	Nef(192–206 BRU)	HHVARELHPEYFKNC	HIV-1 infection	human(A1)	[Hadida (1992)]

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients

Nef( )	Nef( )		HIV-1 infection	human( )	[Wasik (2000)]

- HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of β-chemokines and IL-2 relative to other HIV+ infants
- No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors
- CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccinia/HIV constructs

Nef( )	Nef( )		HIV-1 infection	human( )	[De Maria (1997)]

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T-cell function
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels

Nef( ) Nef( ) HIV-1 infection human( ) [Lubaki (1999)]

- Three strategies were used to analyze CTL activity: area under the net HIV-specific lysis curve (ACU), linear regression (LR) of net specific lysis, and the standard method, lytic units (LU20)
- A correlation between low HIV plasma viral load and increased levels of HIV-specific Gag and Nef CTL activity was observed using ACU and LR, but not LU20

Nef( ) Nef( ) Vaccine human( ) [Gorse (1999)]

Vaccine: *Vector/type:* canarypox prime with rgp120 boost *Strain:* LAI and SF2 *HIV component:* Env, Gag, Pro, Nef, Pro

- The vaccine used was rec canarypox expressing HIV-1 env, gag, pol, nef and protease (vCP300) with or without administration of HIV-1 SF-2 rgp120
- In vitro inducible CTL activity against HIV-1 Env, Gag, Pol, and Nef antigens was observed in 79% (15/19) of vaccine recipients
- The combination of vCP300 and vP1291 together resulted in an overall increase in CTL induction and detection sensitivity

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Nef( ) Nef( ) HIV-1 infection human( ) [Gamberg (1999)]

- 13/13 subjects with advanced HIV infections showed CD8 T-cell proliferation and differentiation of CTL *in vitro*, and six individuals showed HIV-specific responses to Gag, Pol, Env or Nef antigens
- Data suggests that the functional and genetic integrity of the CD8 T-cell repertoire (TCR betaV gene intrafamily genetic diversity) remains intact through advanced HIV infection, although HIV-specific CTL activity decreases

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Nef( ) Nef( ) Vaccine human( ) [Calarota (1999)]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev Tat

- 9/9 HIV-1+ subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-γ production, and IL-6 and IgG responses
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination

---

Nef( ) Nef( ) HIV-1 infection human( ) [Buseyne (1998a)]

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants and: remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load

---

Nef( ) Nef( ) HIV-1 infection human( ) [Buseyne (1998b)]

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes

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Nef( ) Nef( ) Vaccine human( ) [Evans (1999)]

Vaccine: *Vector/type:* canarypox *HIV component:* gp120, gp41, Gag, Pro, Nef, RT

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination

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Nef( ) Nef( ) HIV-1 infection human( ) [da Silva & Hughes(1998)]

- CTL dense regions of Nef tend to lie in conserved domains with low non-synonymous substitution per site – authors consider that this may be due to a host adaptation to infection that focuses the CTL response to be directed against conserved functional domains [da Silva & Hughes(1998)]

Nef( ) Nef( ) HIV-1 infection human( ) [Legrand (1997)]

- Seventeen recently infected patients were tested for CTL response to HIV proteins Env, Gag, Pol, Rev, Nef, Vif and Tat
- An early response (within a month following PI) was noted in 87% of the subjects to Gag, 75% to Env, and 50% to Nef
- Early responses to Pol, Rev, Vif and Tat were rare

Nef( ) Nef( ) HIV-1 infection human( ) [Zerhouni (1997)]

- CTL responses to Env, Gag, Nef and RT were tested at various phases of disease progression – 10 asymptomatic patients generally had CTL responses to all proteins, 10 ARC patients responded well to all proteins except Nef, and AIDS patients had few responses to any proteins

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Nef( ) Nef( ) HIV-1 infection ( ) [Kuiken (1999)]

- A correlation between conserved regions of Nef and CTL epitope density was also noted in [Kuiken (1999)]. The authors suggest that this may be due to biological reasons such as the one described above [da Silva & Hughes(1998)], or due to epitope processing, or may possibly be an artifact of experimental strategy for epitope definition such that conserved epitopes would tend to be identified because they would be more likely to be cross-reactive with the test reagents
- Both p17 and Nef show a correlation between epitope density and conserved regions in the protein – in contrast, p24 is a more conserved protein and known epitopes are evenly distributed across p24

Nef( ) Nef( ) HIV-1 infection human( ) [Aladdin (1999)]

- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death

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Nef( ) Nef( ) HIV-1 infection human( ) [Jin (1998a)]

- CTL precursor frequencies were determined in HIV-1 infected pregnant women, and higher CTLp frequencies to Pol and SF2 Nef, but not IIIB Nef, were found in non-transmitting mothers than in transmitting mothers – Nef CTL responses have been found in uninfected infants born to HIV+ women (Lazuriaga95);

Nef( ) ( ) human( ) [Novitsky (2001)]

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort
- 37/45 subjects (82%) demonstrated Nef specific ELISPOT CTL responses of more than 100 SFC/106 PBMC
- Two Nef-immunodominant regions were identified, one spanned amino acid positions 67 to 96 using HXB2 numbering system while the second corresponded to amino acid positions 122 to 141

- While there was some subtype B and C cross-reactivity, there was greater breadth and intensity of response if the CTL from HIV-1-infected individuals was probed with ELISPOT using peptides derived from the same subtype (a median of three Nef epitopes recognized within subtype C compared with one Nef epitope recognized from subtype B peptides, and ELISPOT results with a median of 763 SFC/106 PBMC among responses to HIV-1 C, versus a median of 318 SFC/106 PBMC among responses to HIV-1 B

Nef( ) Nef( ) HIV-1 infection human( ) [Cao (2000)]

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent-specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype

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Nef( ) Nef( ) HIV-1 infection, Vaccine human( ) [Calarota & Wahren(2001)]

Vaccine: *Vector/type:* DNA *HIV component:* Nef, Rev, Tat *Stimulatory Agents:* CpG motifs

- This review discusses the cellular immune response, and comments on the stimulatory role of CpG motifs and how HIV-1 DNA vaccines can boost the CTL and Th proliferative responses in asympotomatic HIV+ individuals

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Nef( ) Nef( ) HIV-1 infection human(A*0201, Cw*08) [Shacklett (2000)]

- HIV-1 specific, MHC class I-restricted CTL killing was detected in duodenal and rectal gut associated lymphoid tissue (GALT) sites from three infected individuals – the distribution of class I restricted CTL was different in the peripheral blood samples and GALT samples

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Nef( ) Nef( ) Vaccine murine(H-2D^d) [Collings (1999)]

Vaccine: *Vector/type:* DNA *Strain:* BRU *HIV component:* nef

- A comparison of DNA vaccination with HIV-1 Nef expression vectors pBN-CMV-NEF and pBN-RSV-NEF (self-replicating), pCGE2-NEF (non-replicating).
- CTL immune responses were detected using all three expression vectors, while a humoral immune response to Nef was only observed in the self-replicating expression vectors; possibly antibody responses require higher levels of protein expression

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Nef( ) Nef(139–147 HXB3) LTFGWCFKL Vaccine murine(HLA-A201 transgenic) [Sandberg (2000)]

Vaccine: *Vector/type:* DNA, peptide *Strain:* HXB3 *HIV component:* Nef *Stimulatory Agents:* Freund's adjuvant

- Ten Nef 9-mer peptides were predicted to have a strong binding affinity with HLA-A*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly
- A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with either nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by gene gun – LTFGWCFKL did not elicit a CTL response

- LTFGWCFKL was also tested by subcutaneous injection of Nef peptides in Freund's adjuvant, because it bound strongly to HLA-A*0201, and the peptide vaccination did elicit a response
- The lack of response to the nef DNA vaccine and the response to the peptide suggests LTFGWCFKL may not be processed

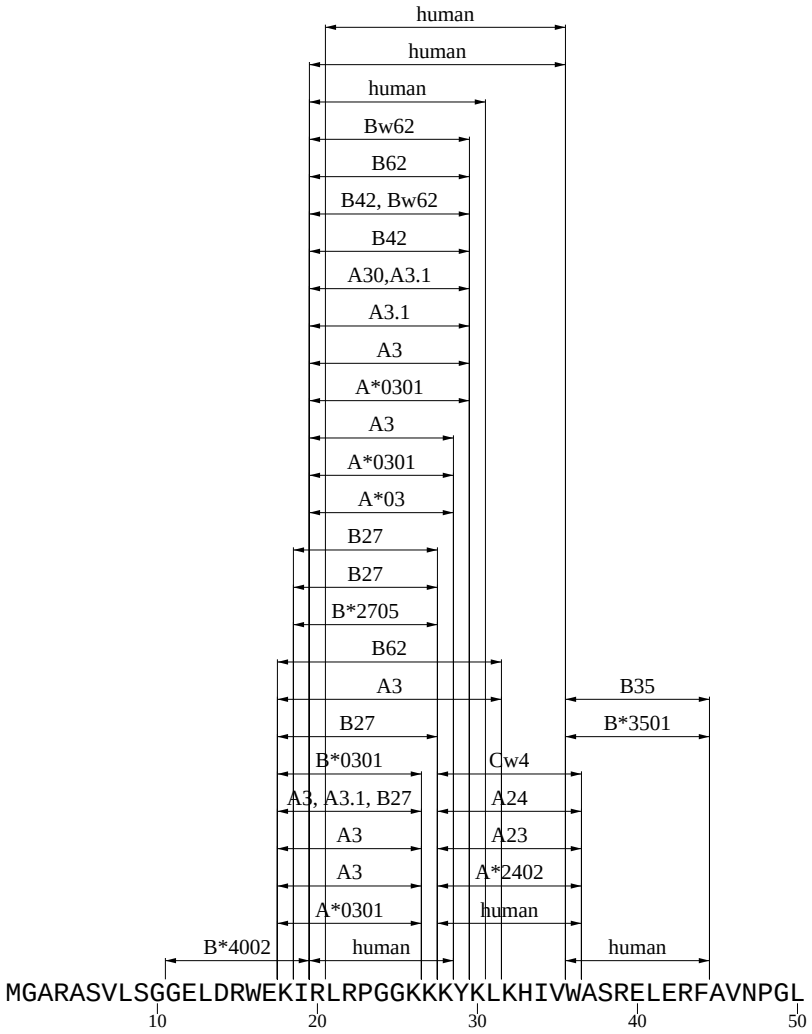
Nef( )	Nef( )	SIV Nef and Env CTL epitopes	SIV infection	Rhesus macaque(Mamu-A*11, -B*03, -B*04, and -B*17)	[Dzuris (2000)]

- Cell binding assays for Mamu molecules were employed to describe the peptide binding motifs for Mamu-A*11, -B*03, -B*03, -B*04, and -B*17 CTL epitopes – a similarity for Mamu-A*11 and -B*03 and human HLA-B*44 and -B*27, respectively, was observed – all epitopes studied were SIV epitopes, so not specifically listed here

Part II-B: Maps of CTL Epitope Locations Plotted by Protein

Only epitopes <22 amino acids long are shown. If HLA specificity was not determined but the CTL response was in a person, the reactive peptide is listed as "human", otherwise the HLA presenting molecule is noted. The non-human CTL responses have the organism listed.

p17 CTL Map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human
human
Bw62
B62
B42, Bw62
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A3.1
A3
A*0301
A3
A*0301
A*03
B27
B27
B*2705
B62
A3
B27
B*0301
A3, A3.1, B27
A3
A3
A*0301
B*4002
human
B35
B*3501
Cw4
A24
A23
A*2402
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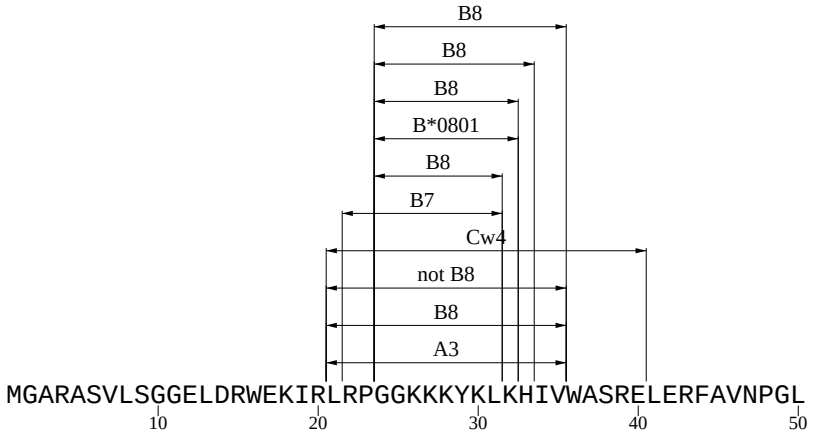
20
30
40
50


B8
B8
B8
B*0801
B8
B7
Cw4
not B8
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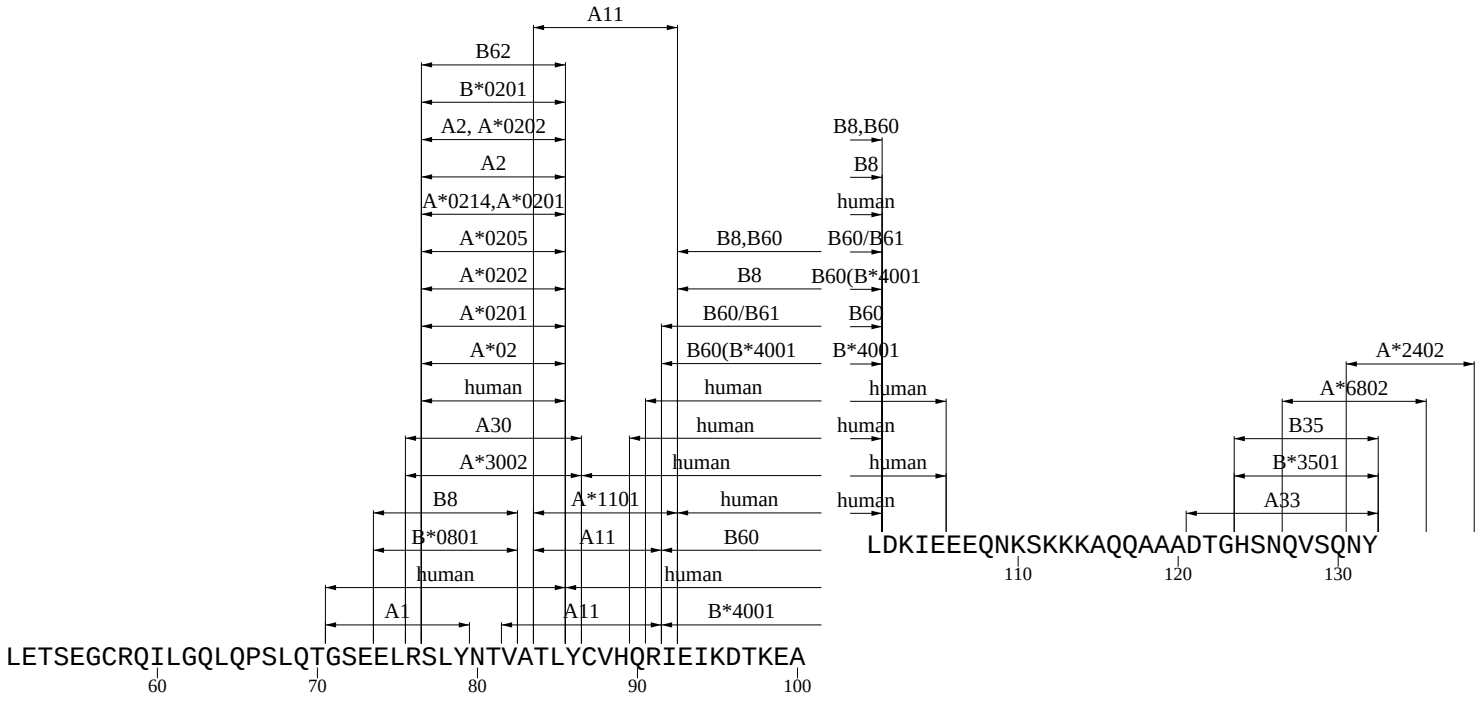
10
20
30
40
50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A*0201
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B8
B*0801
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A*6802
B35
B*3501
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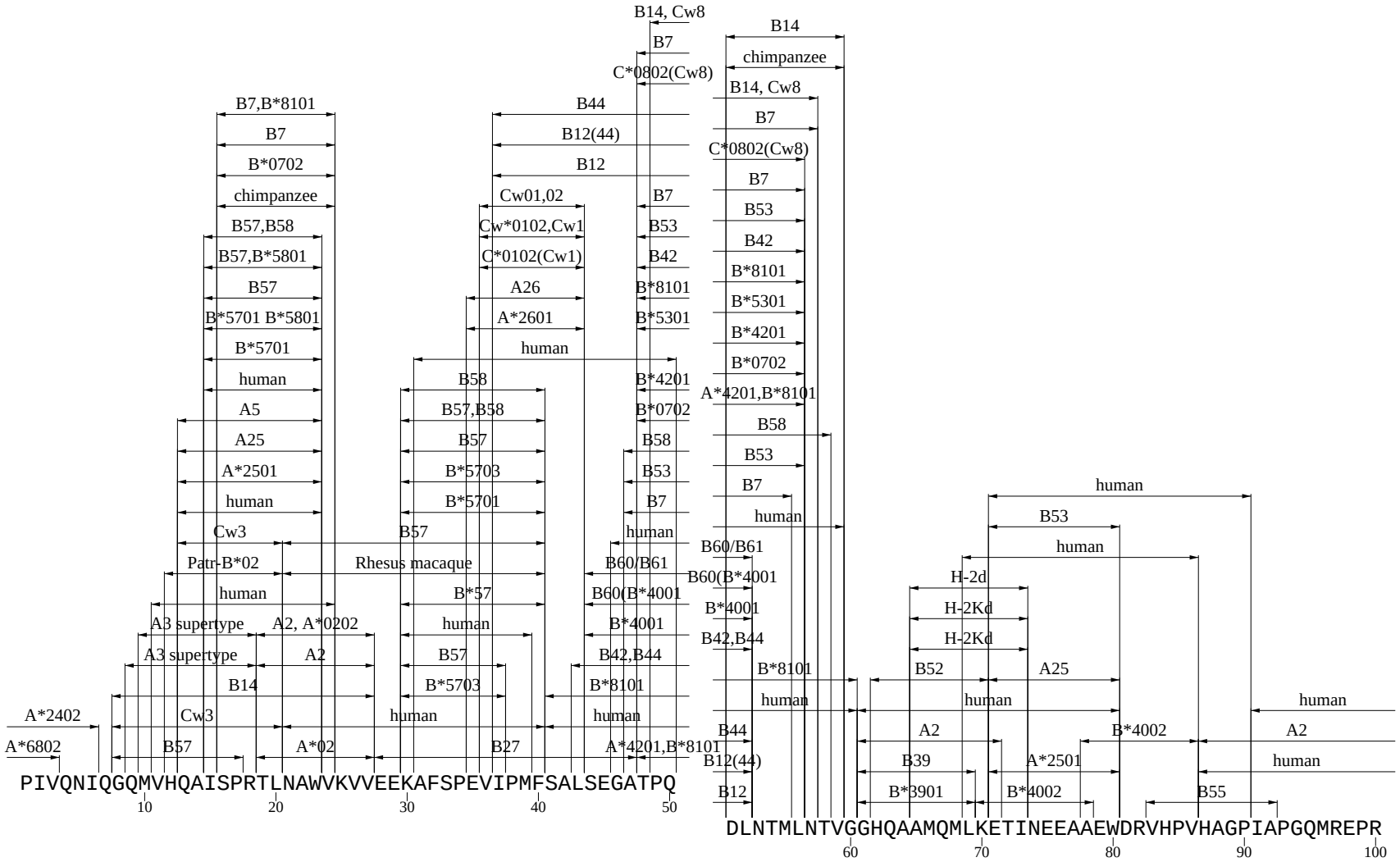
p24 CTL Map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C*0802(Cw8)
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B57,B58
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A25
A*2501
human
Cw3
Patr-B*02
human
A3 supertype
A3 supertype
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A*6802
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B*5703
Cw3
human
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B53
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B7
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B7
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human
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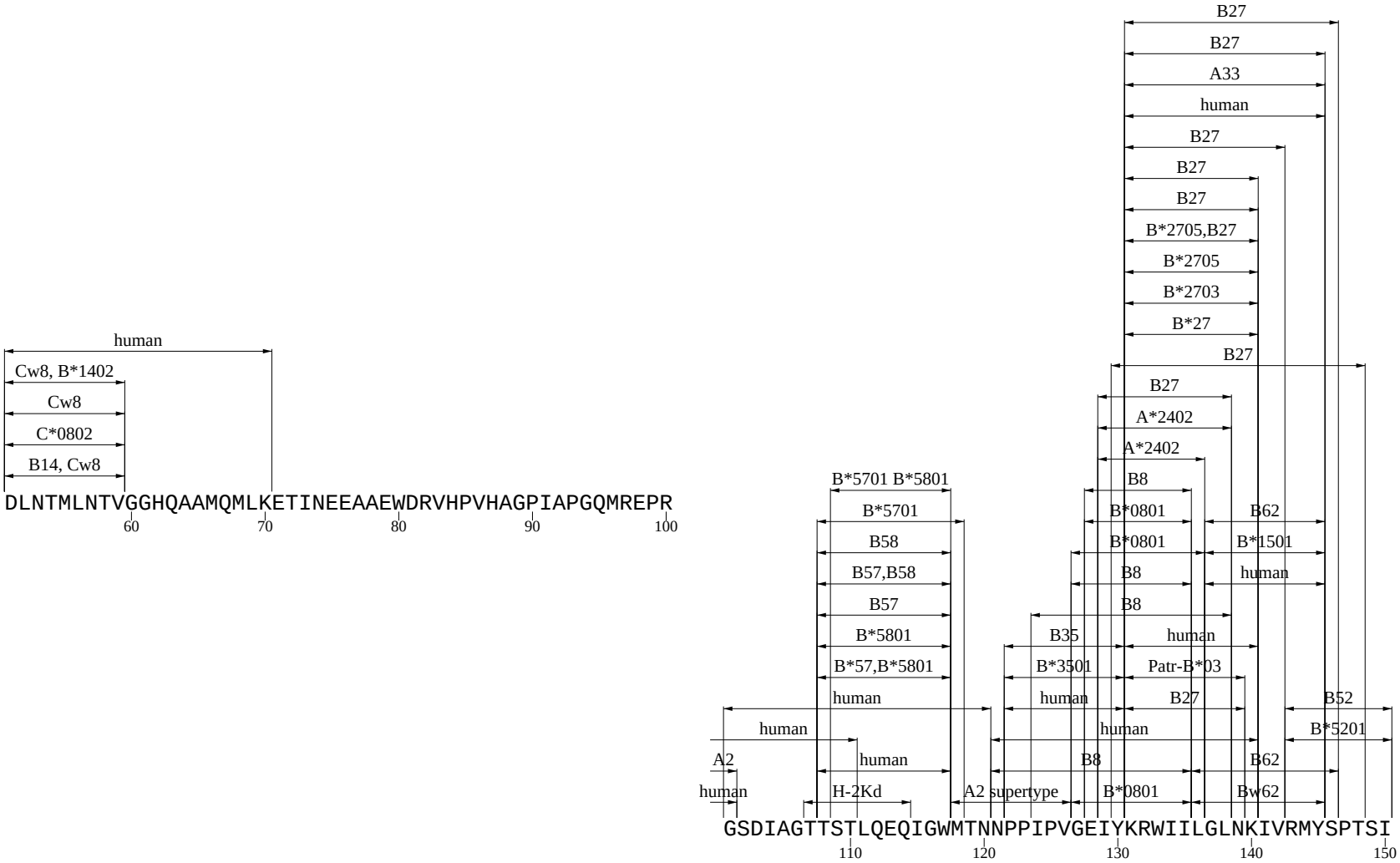
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Cw8
C*0802
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80
90
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B27
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B*27
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B27
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Patr-B*03
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B8
B62
human
H-2Kd
A2 supertype
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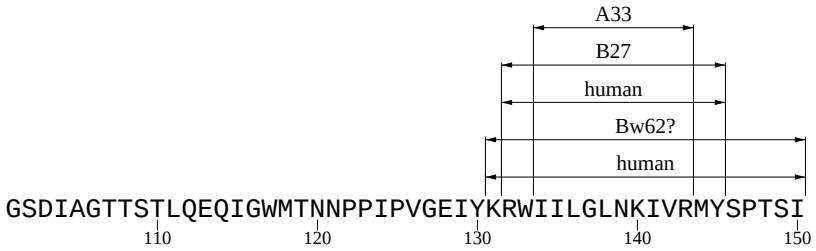
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Bw62?
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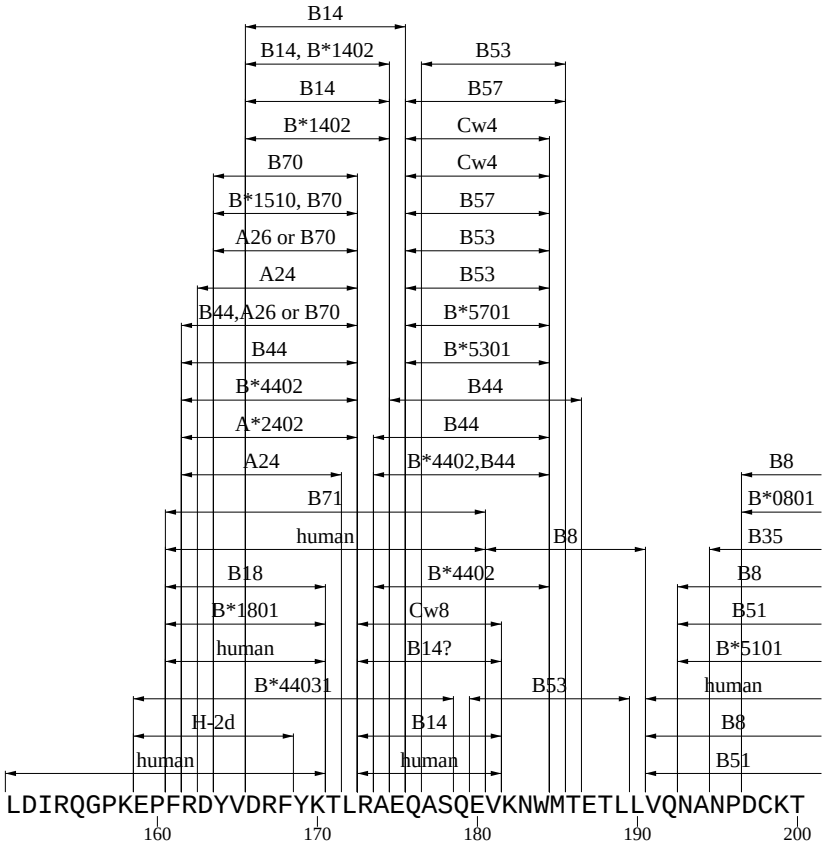
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B14
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B*1402
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B*1510, B70
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A26 or B70
B53
A24
B53
B44,A26 or B70
B*5701
B44
B*5301
B*4402
B44
A*2402
B44
A24
B*4402,B44
B8
B71
B*0801
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B8
B35
B18
B*4402
B8
B*1801
Cw8
B51
human
B14?
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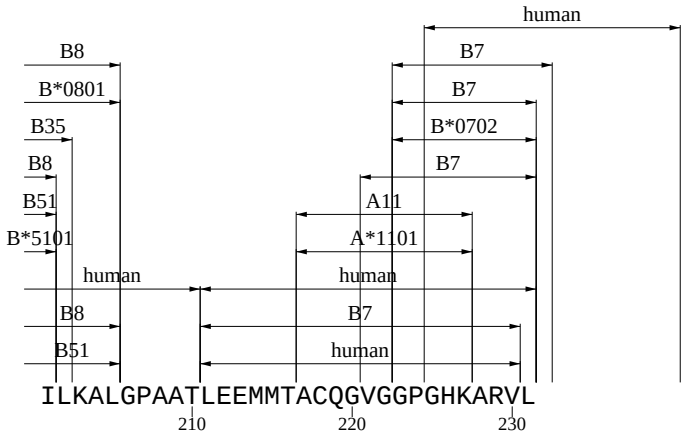
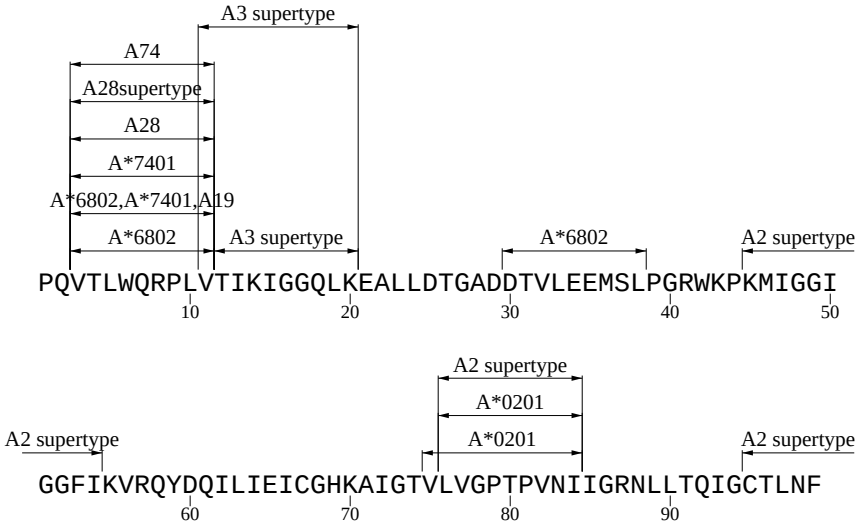
B*44031
B53
human
H-2d
B14
B8
human
human
B51
LDIRQGPKEPFRDYVDRFYKTLRAEQASQEVKNWMTETLLVQNANPDCKT
160
170
180
190
200


human
B8
B7
B*0801
B7
B35
B*0702
B8
B7
B51
A11
B*5101
A*1101
human
human
B8
B7
B51
human
ILKALGPAATLEEMMTACQGVGGPGHKARVL
210
220
230

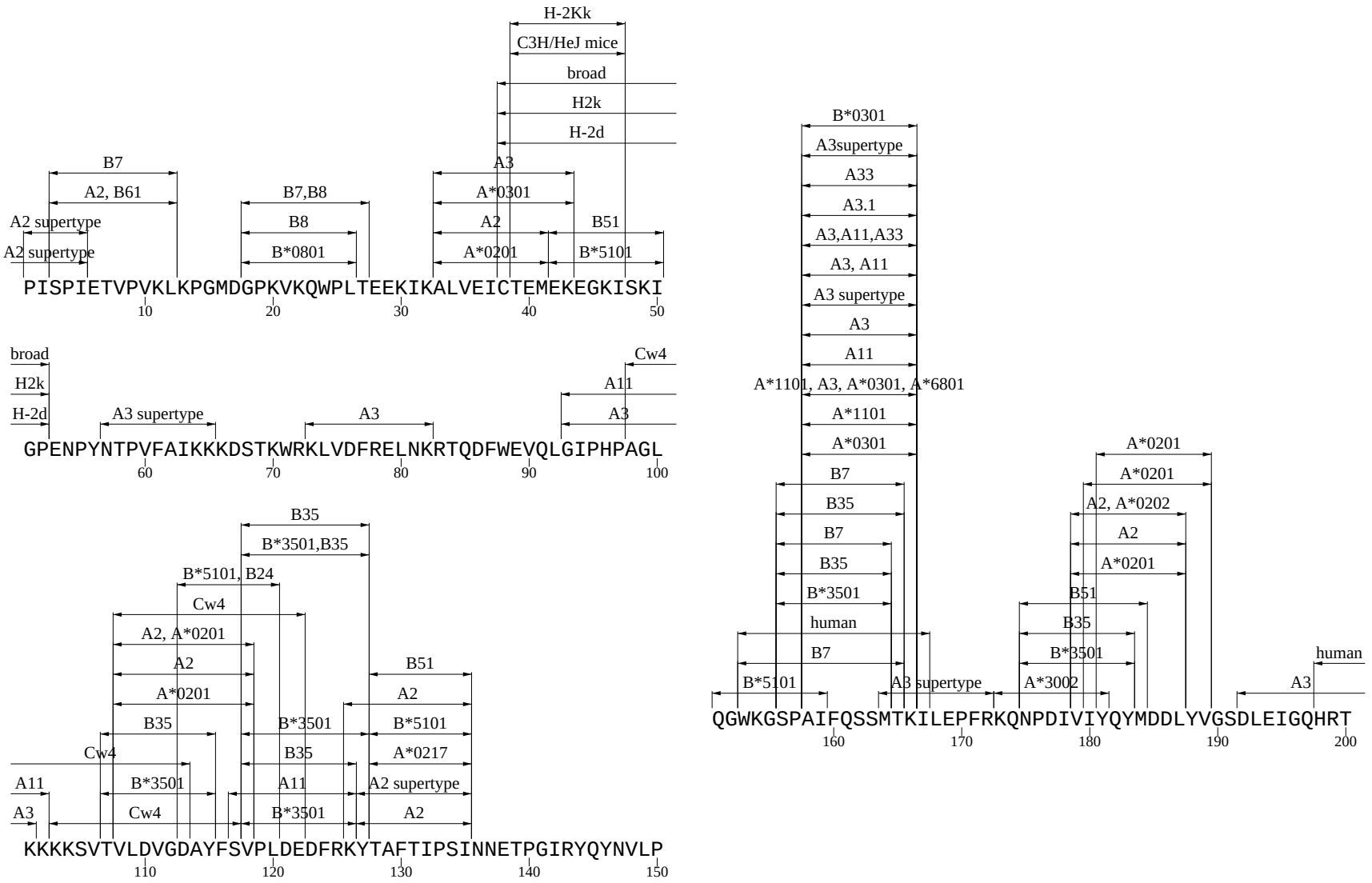
p2p7p1p6 CTL Map

Protease CTL Map



CTL

RT CTL Map


H-2Kk
C3H/HeJ mice
broad
H2k
H-2d
B7
A2, B61
A2 supertype
A2 supertype
B7,B8
B8
B*0801
A3
A*0301
A2
A*0201
B51
B*5101
PISPIETVPVKLKPGMDGPKVKQWPLTEEKIKALVEICTEMEKEGKISKI
10
20
30
40
50
broad
H2k
H-2d
A3 supertype
A3
Cw4
A11
A3
GPENPYNTPVFAIKKKDSTKWRKLVDFRELNKRTQDFWEVQLGIPHPAGL
60
70
80
90
100
B35
B*3501,B35
B*5101, B24
Cw4
A2, A*0201
A2
A*0201
B35
B*3501
B51
A2
B*3501
B*5101
Cw4
B35
A*0217
A11
B*3501
A11
A2 supertype
A3
Cw4
B*3501
A2
KKKKSVTVLDVGDAYFSVPLDEDFRKYTAFTIPSINNETPGIRYQYNVLP
110
120
130
140
150
B*0301
A3supertype
A33
A3.1
A3,A11,A33
A3, A11
A3 supertype
A3
A11
A*1101, A3, A*0301, A*6801
A*1101
A*0301
B7
B35
B7
B35
B*3501
human
B7
B*5101
A3 supertype
A*0201
A*0201
A2, A*0202
A2
A*0201
B51
B35
B*3501
A*3002
human
A3
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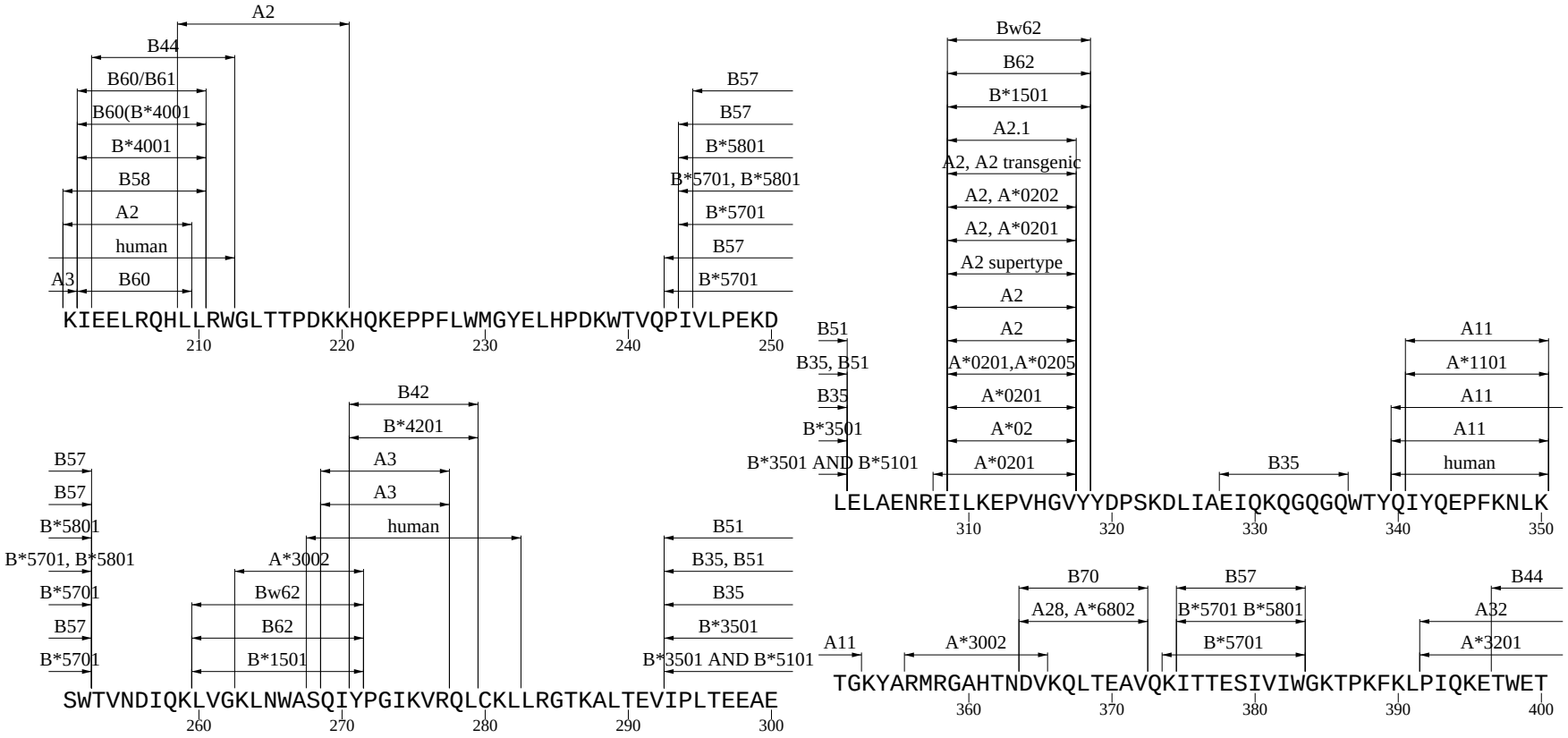
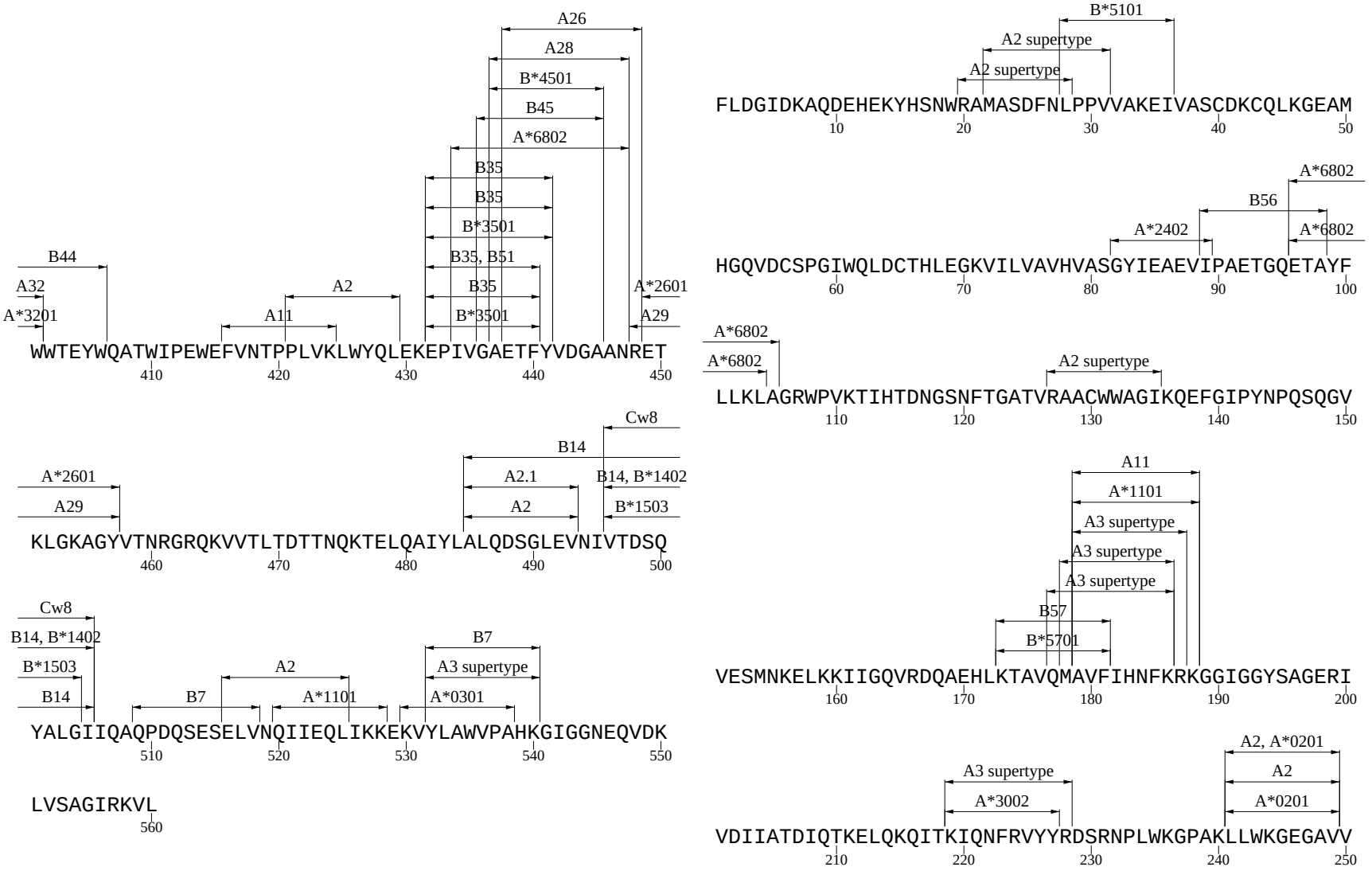
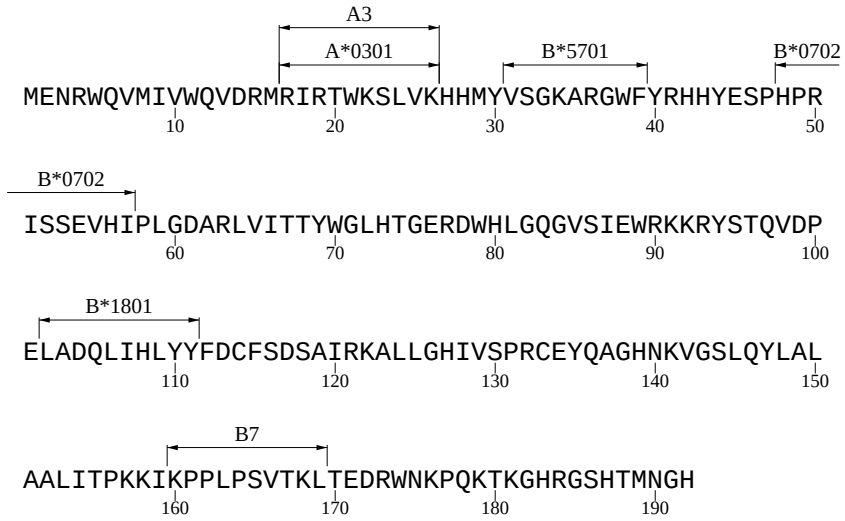
160
170
180
190
200

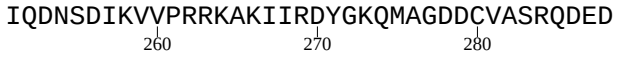

A2
B44
B60/B61
B60(B*4001
B*4001
B58
A2
human
A3
B60
B57
B57
B*5801
B*5701, B*5801
B*5701
B57
B*5701
KIEELRQHLLRWGLTTPDKKHQKEPPFLWMGYELHPDKWTVQPIVLPEKD
210
220
230
240
250
Bw62
B62
B*1501
A2.1
A2, A2 transgenic
A2, A*0202
A2, A*0201
A2 supertype
A2
A2
A*0201,A*0205
A*0201
A*02
A*0201
B51
B35, B51
B35
B*3501
B*3501 AND B*5101
A11
A*1101
A11
A11
human
B35
LELAENREILKEPVHGVYYDPSKDLIAEIQKQGQGQWTYQIYQEPFKNLK
310
320
330
340
350
B42
B*4201
B57
B57
B*5801
B*5701, B*5801
B*5701
B57
B*5701
A3
A3
human
A*3002
Bw62
B62
B*1501
B51
B35, B51
B35
B*3501
B*3501 AND B*5101
SWTVNDIQKLVGKLNWASQIYPGIKVRQLCKLLRGTKALTEVIPLTEEAE
260
270
280
290
300
B70
A28, A*6802
B57
B*5701 B*5801
B*5701
B44
A32
A*3201
A11
A*3002
TGKYARMRGAHTNDVKQLTEAVQKITTESIVIWGKTPKFKLPIQKETWET
360
370
380
390
400

Integrase CTL Map



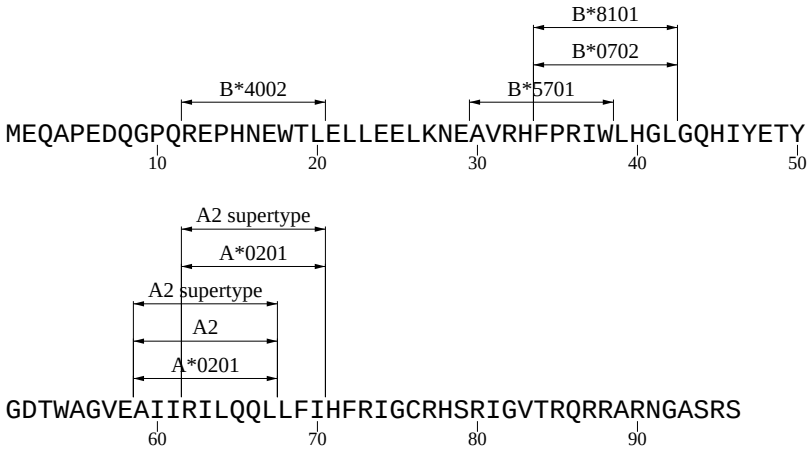
Vif CTL Map



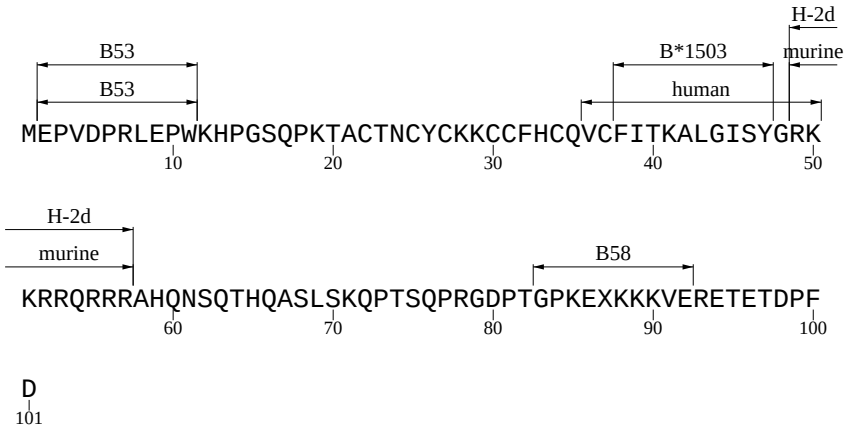


CTL

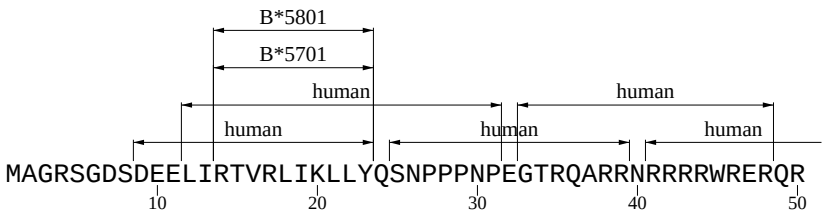
Vpr CTL Map

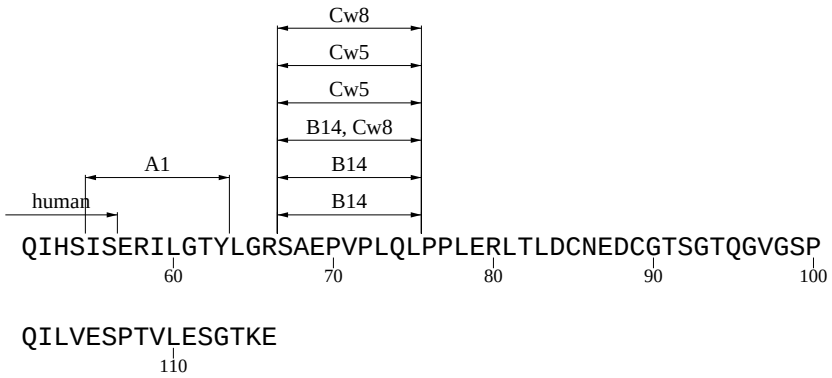


Tat CTL Map

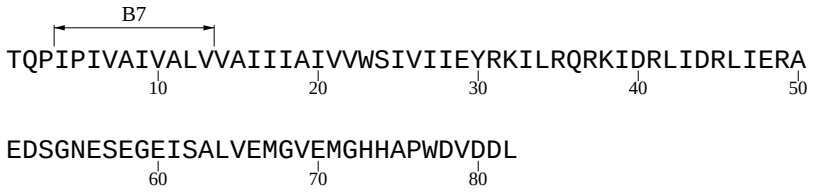


Rev CTL Map



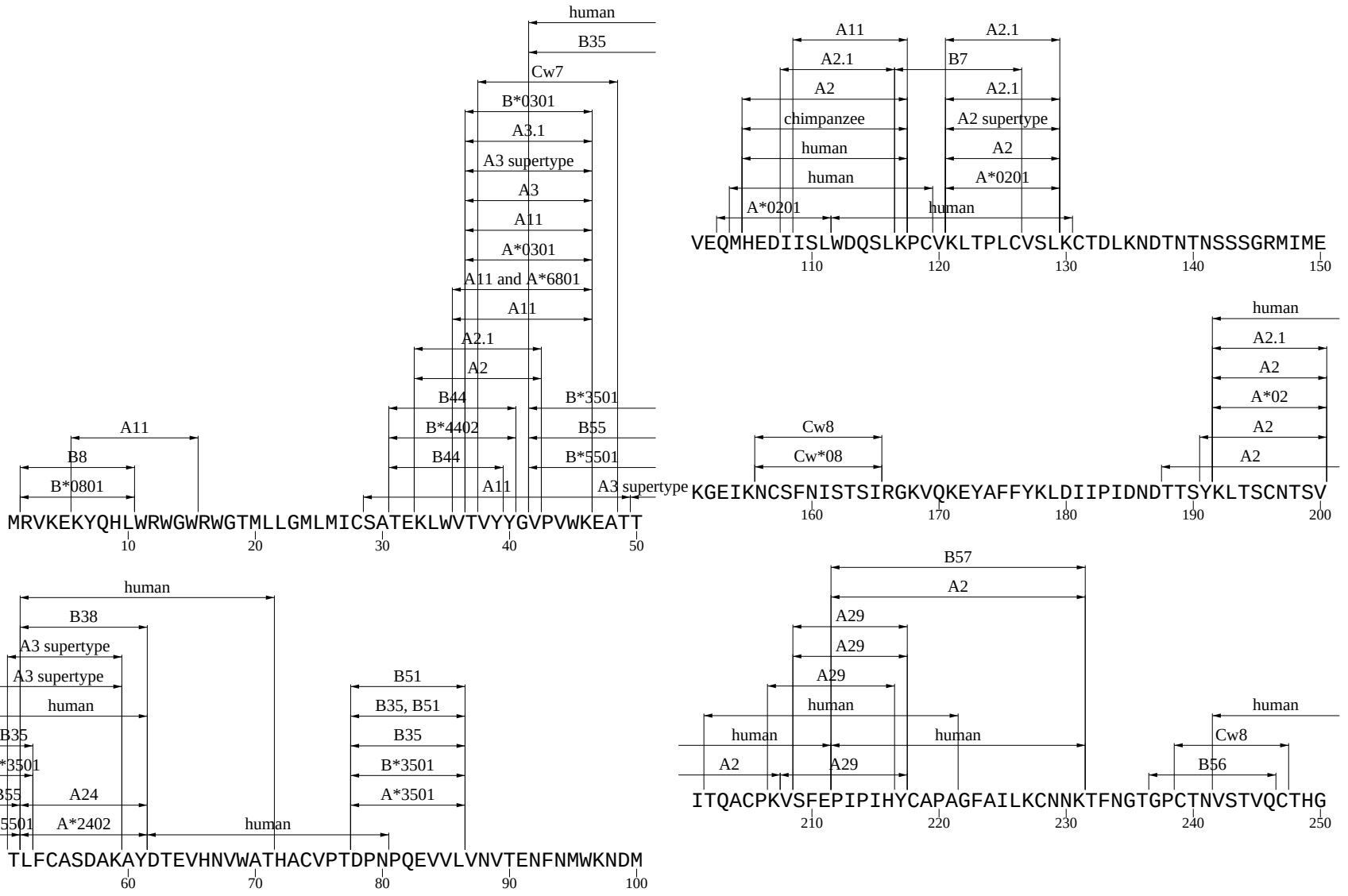


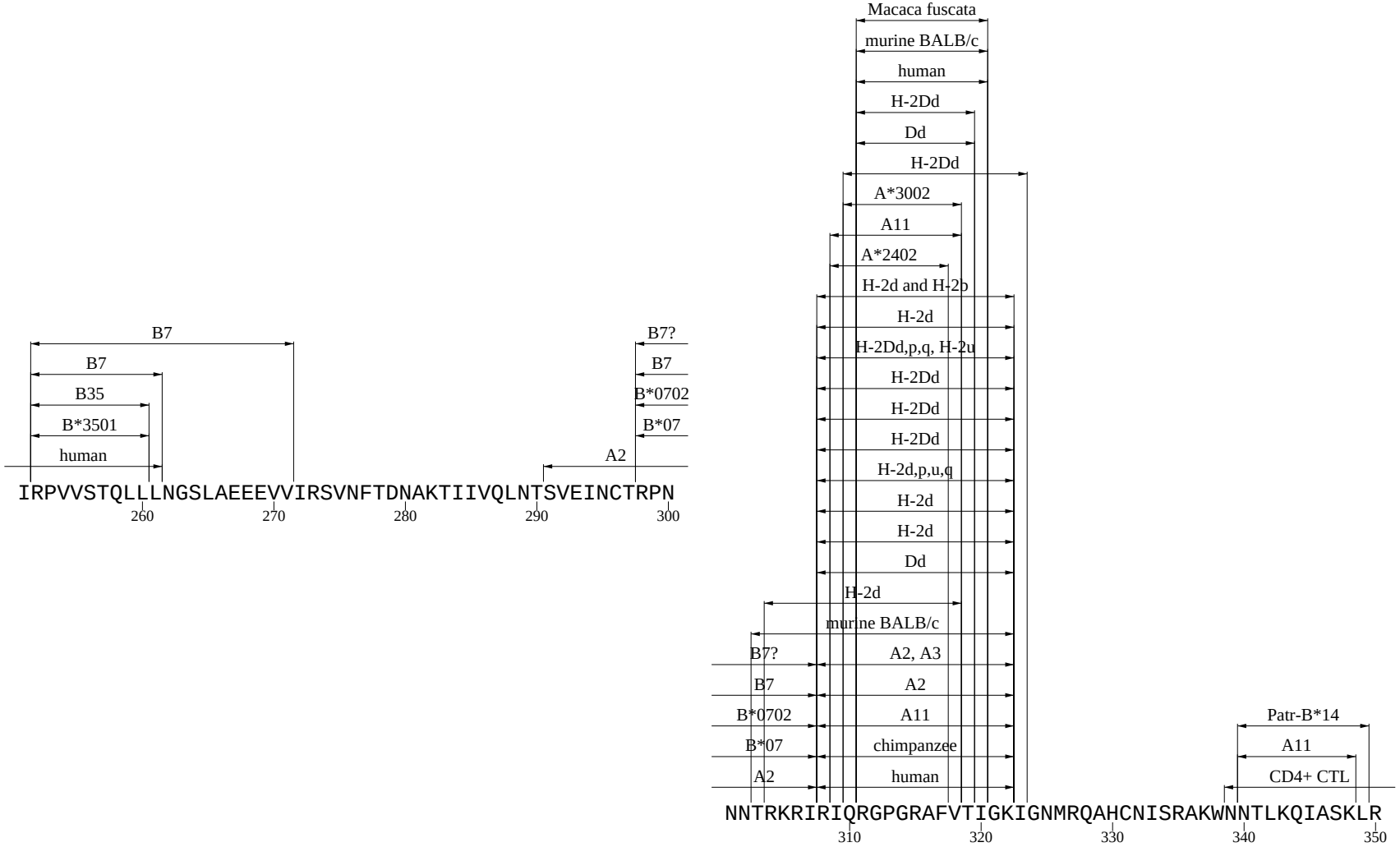
Vpu CTL Map

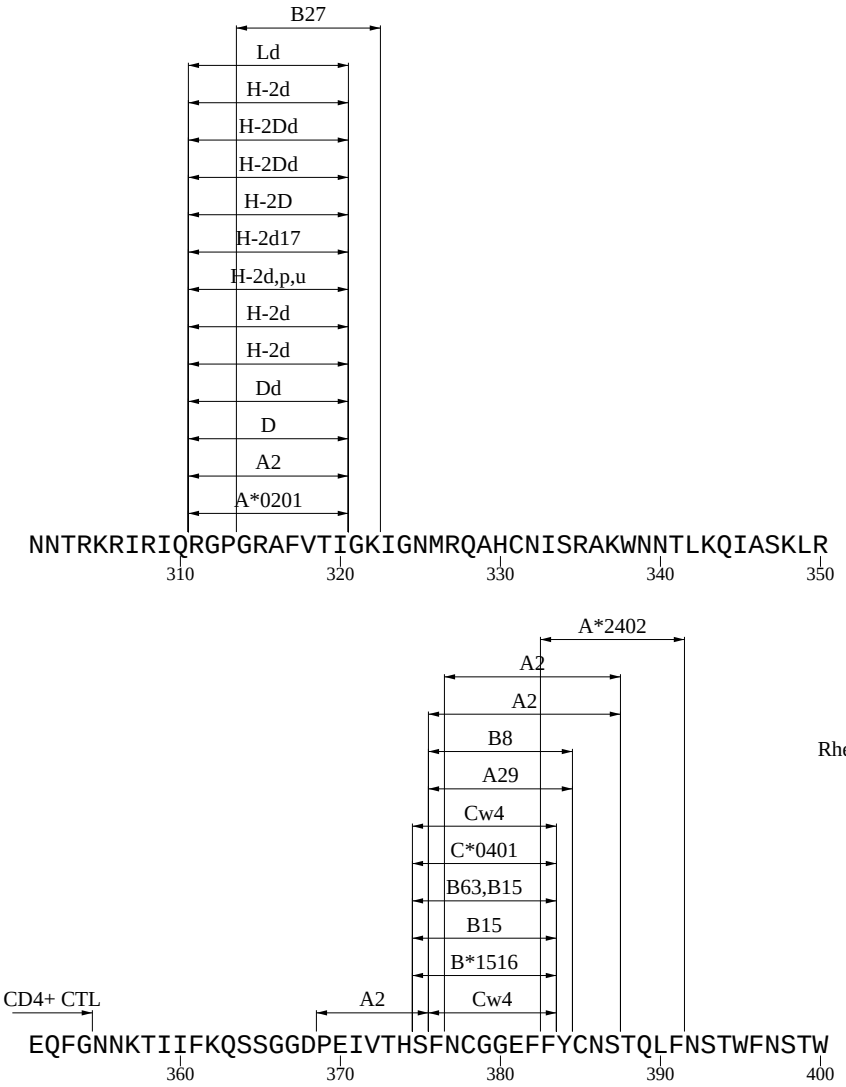


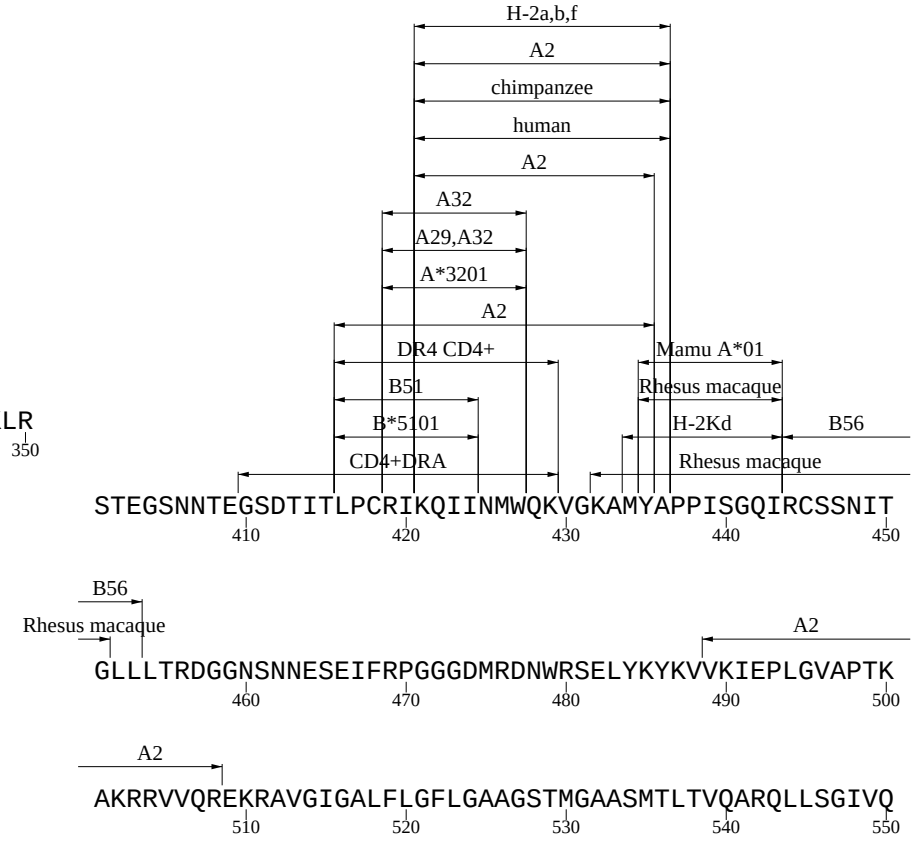
CTL

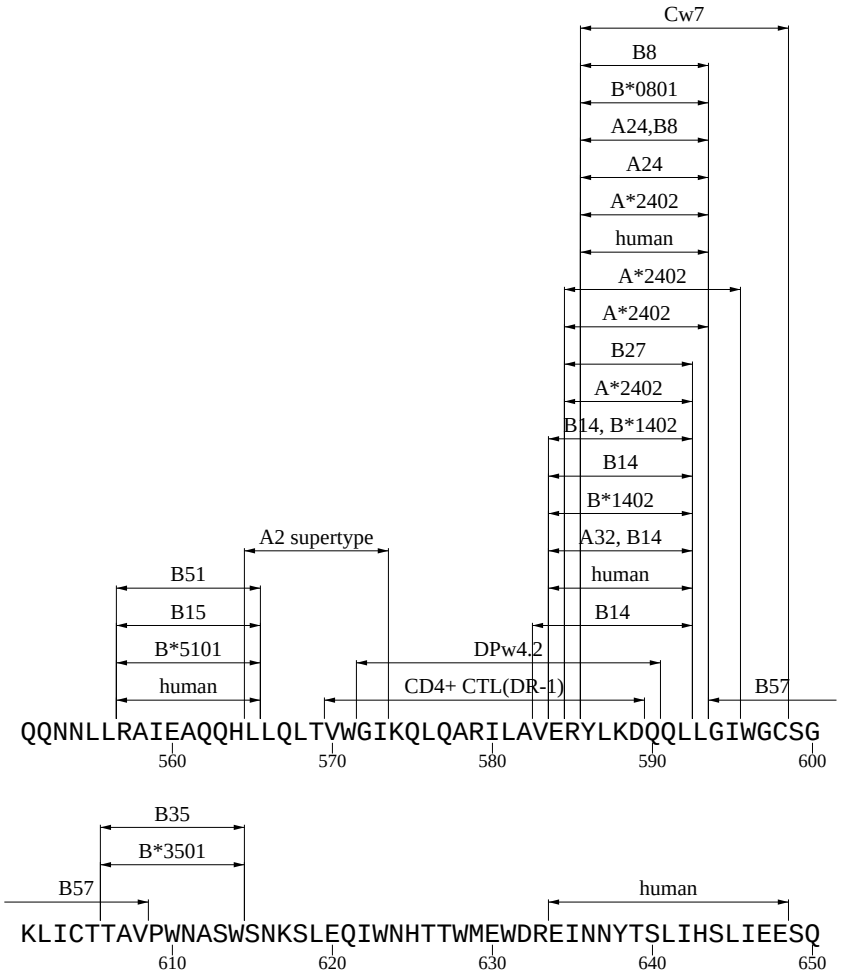
gp160 CTL Map

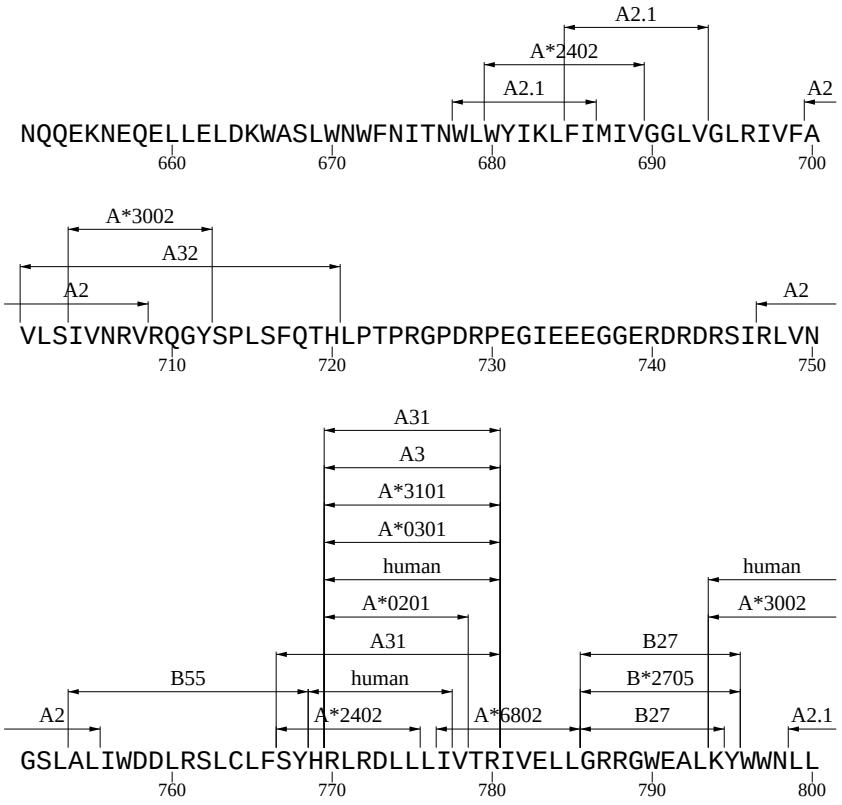



B7
B7
B35
B*3501
human
B7?
B7
B*0702
B*07
A2
IRPVVSTQLLLNGSLAEEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPN
260
270
280
290
300
Macaca fuscata
murine BALB/c
human
H-2Dd
Dd
H-2Dd
A*3002
A11
A*2402
H-2d and H-2b
H-2d
H-2Dd,p,q, H-2u
H-2Dd
H-2Dd
H-2Dd
H-2d,p,u,q
H-2d
H-2d
Dd
H-2d
murine BALB/c
B7?
A2, A3
B7
A2
B*0702
A11
B*07
chimpanzee
A2
human
Patr-B*14
A11
CD4+ CTL
NNTRKRIRIQRGPGRAFVTIGKIGNMRQAHCNISRAKWNNTLKQIASKLR
310
320
330
340
350


B27
Ld
H-2d
H-2Dd
H-2Dd
H-2D
H-2d17
H-2d,p,u
H-2d
H-2d
Dd
D
A2
A*0201
NNTRKRIRIQRGPGRAFVTIGKIGNMRQAHCNISRAKWNNTLKQIASKLR
310
320
330
340
350
A*2402
A2
A2
B8
A29
Cw4
C*0401
B63,B15
B15
B*1516
Cw4
CD4+ CTL
A2
EQFGNNKTIIFKQSSGGDPEIVTHSFNCGGEFFYCNSTQLFNSTWFNSTW
360
370
380
390
400

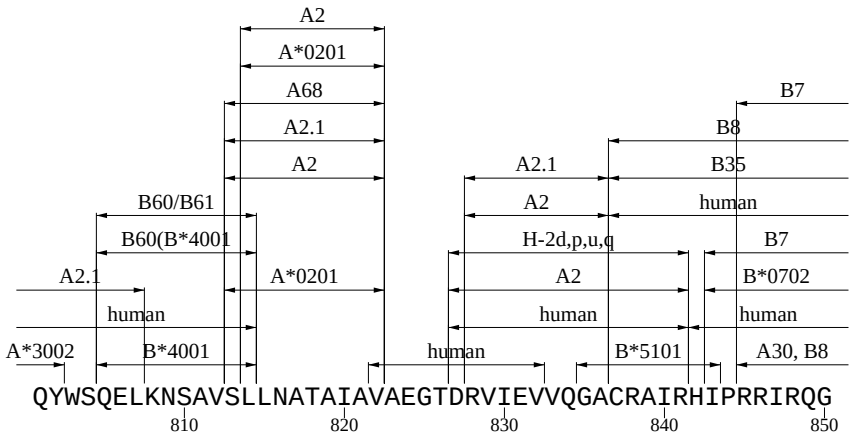

H-2a,b,f
A2
chimpanzee
human
A2
A32
A29,A32
A*3201
A2
DR4 CD4+
Mamu A*01
B51
Rhesus macaque
B*5101
H-2Kd
B56
CD4+DRA
Rhesus macaque
STEGSNNTEGSDTITLPCRIKQIINMWQKVGKAMYAPPISGQIRCSSNIT
410
420
430
440
450
B56
Rhesus macaque
A2
GLLLTRDGGNSNNESEIFRPGGGDMRDNWRSELYKYKVVKIEPLGVAPTK
460
470
480
490
500
A2
AKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQ
510
520
530
540
550

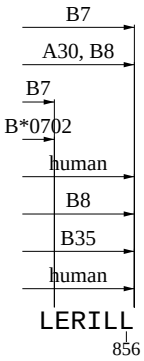

Cw7
B8
B*0801
A24,B8
A24
A*2402
human
A*2402
A*2402
B27
A*2402
B14, B*1402
B14
B*1402
A32, B14
human
B14
A2 supertype
B51
B15
B*5101
human
DPw4.2
CD4+ CTL(DR-1)
B57
QQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLGIWGCSG
560
570
580
590
600
B35
B*3501
B57
human
KLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHSLIEESQ
610
620
630
640
650

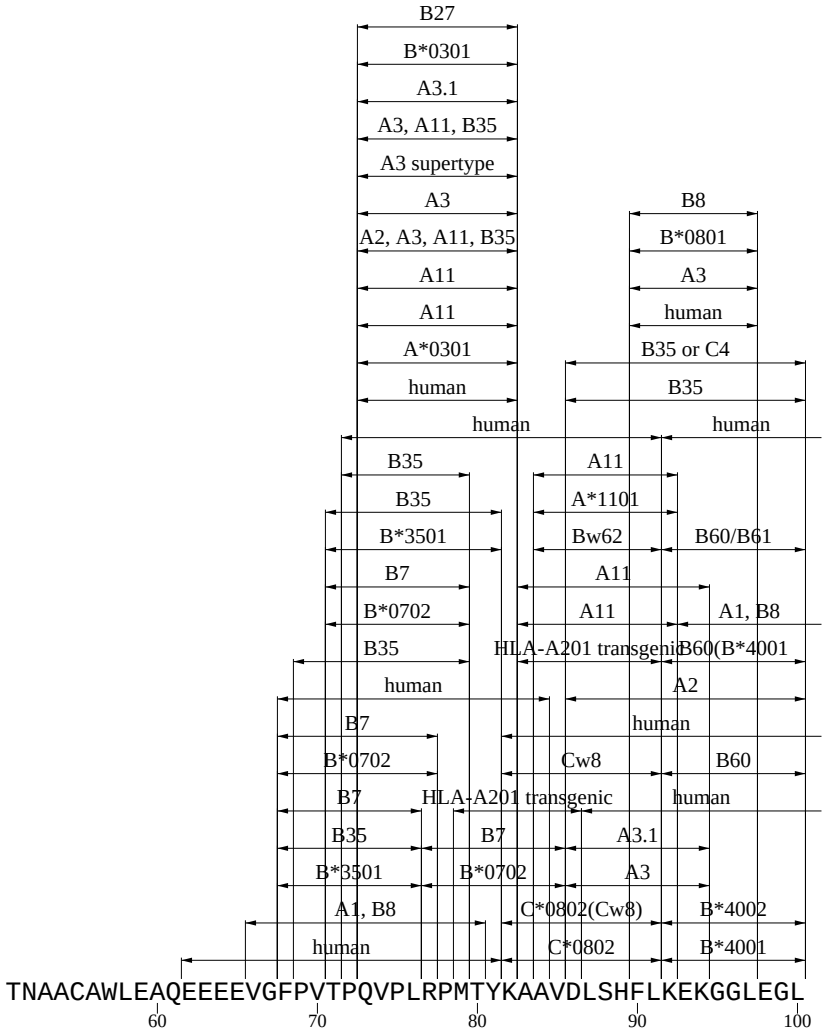

A2.1
A*2402
A2.1
A2
NQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRIVFA
660
670
680
690
700
A*3002
A32
A2
A2
VLSIVNRVRQGYSPLSFQTHLPTPRGPDRPEGIEEEGGERDRDRSIRLVN
710
720
730
740
750
A31
A3
A*3101
A*0301
human
A*0201
A31
B55
human
A2
A*2402
A*6802
human
A*3002
B27
B*2705
B27
A2.1
GSLALIWDDLRSLCLFSYHRLRDLLLIVTRIVELLGRRGWEALKYWWNLL
760
770
780
790
800

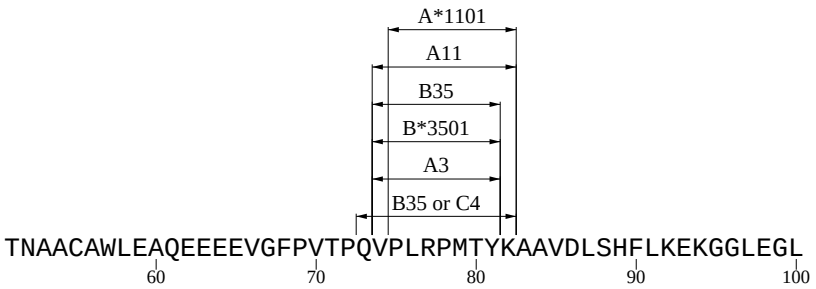
Nef CTL Map


B8
B*0801
HLA-A201 transgenic
MGGKWSKSSVIGWPTVRERMRRAEPAADRVGAASRDLEKHGAITSSNTAA
10
20
30
40
50

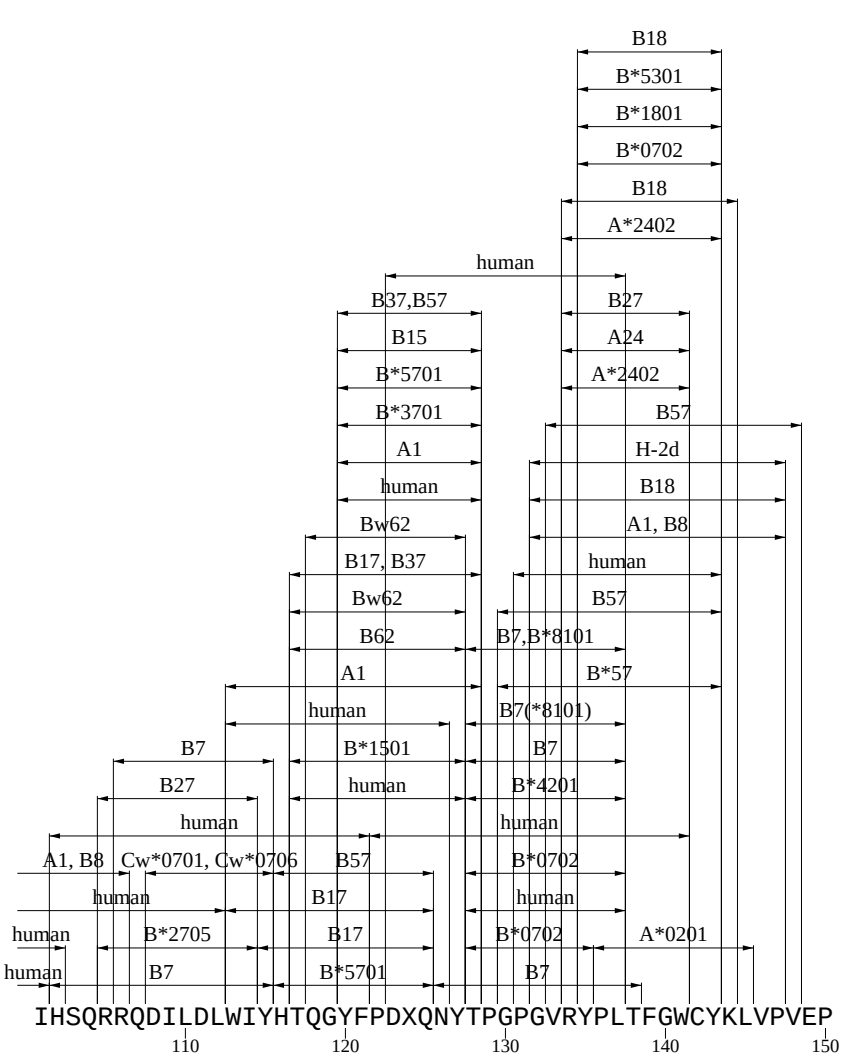

A2
A*0201
A68
A2.1
A2
B60/B61
B60(B*4001
A2.1
A*0201
human
A*3002
B*4001
A2
A2.1
A2
human
H-2d,p,u,q
A2
human
human
B7
B8
B35
human
B7
B*0702
human
A30, B8
B*5101
QYWSQELKNSAVSLLNATAIAVAEGTDRVIEVVQGACRAIRHIPRRIRQG
810
820
830
840
850

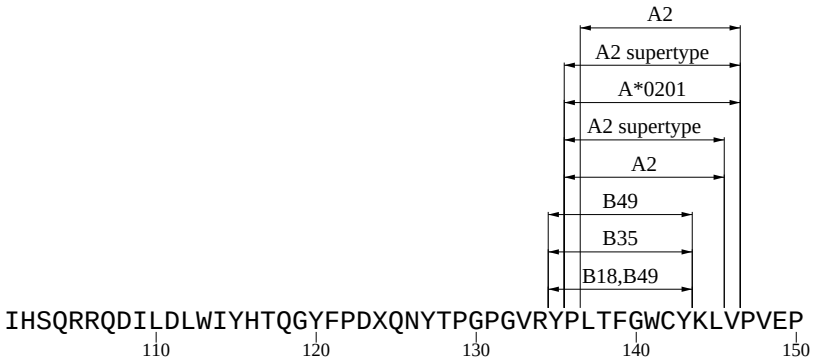

B7
A30, B8
B7
B*0702
human
B8
B35
human
LERILL
856

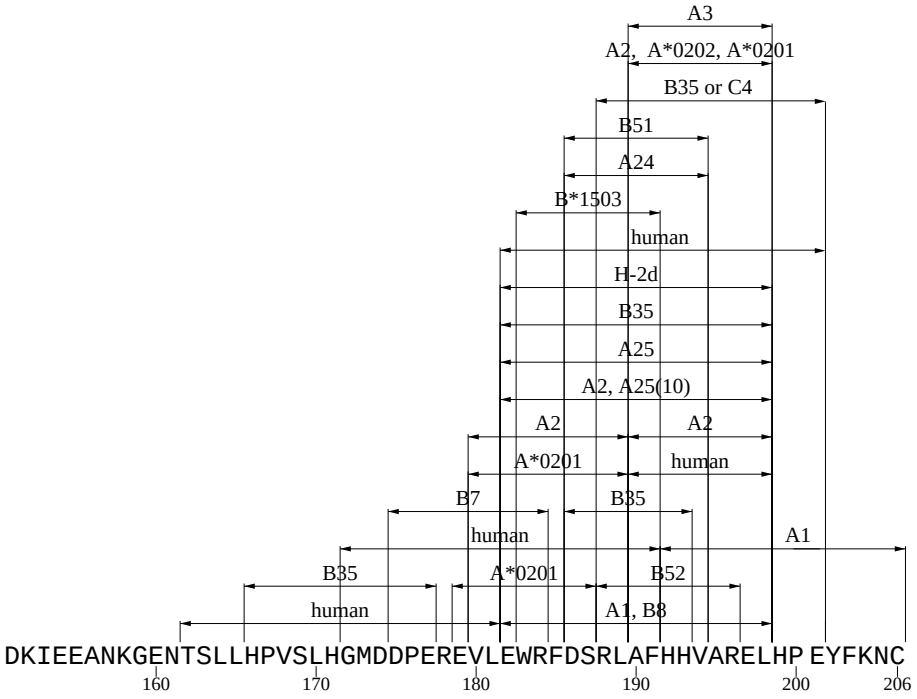

B27
B*0301
A3.1
A3, A11, B35
A3 supertype
A3
A2, A3, A11, B35
A11
A11
A*0301
human
B35
B*3501
B7
B*0702
B35
human
B7
B*0702
B7
B35
B*3501
A1, B8
human
B8
B*0801
A3
human
B35 or C4
B35
human
A11
A*1101
Bw62
A11
A11
HLA-A201 transgenic
A2
human
Cw8
HLA-A201 transgenic
B7
A3.1
B*0702
A3
C*0802(Cw8)
C*0802
human
B60/B61
A1, B8
B60(B*4001
B*4002
B*4001
TNAACAWLEAQEEEEVGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGLEGL
60
70
80
90
100


A*1101
A11
B35
B*3501
A3
B35 or C4
TNAACAWLEAQEEEEVGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGLEGL
60
70
80
90
100

HIV CTL Protein Maps







Part II-C: CTL References

[Achour (1996)] A. Achour, F. Bex, P. Hermans, A. Burny, & D. Zagury. Induction of anti-gp160 cytotoxic T cells cross-reacting with various V3 loop P18 peptides in human immunodeficiency virus type 1 envelope-immunized individuals. *J Virol* **70**:6741–6750, 1996.

[Achour (1994)] A. Achour, S. Lemhammedi, O. Picard, J. P. M'Bika, J. F. Zagury, Z. Moukrim, A. Willer, F. Beix, A. Burny, & D. Zagury. Cytotoxic T lymphocytes specific for HIV-1 gp160 antigen and synthetic P18IIIB peptide in an HLA-A11-immunized individual. *AIDS Res Hum Retroviruses* **10**:19–25, 1994. CTL restricted by several different class I molecule HLA types can present this V3 antigen: RIQRGPGRAFVTIGK, HLA A11.

[Achour (1993)] A. Achour, O. Picard, J. P. M'Bika, A. Willer, R. Snart, B. Bizini, C. Carell, A. Burny, & D. Zagury. Envelope protein and P18 IIIB peptide recognized by cytotoxic T lymphocytes from humans immunized with AIDS virus envelope. *Vaccine* **11**:699–701, 1993. Both HLA A2 and A3 class I molecule types can present this V3 antigen: RIQRGP-GRAFVTIGK .

[Achour (1990)] A. Achour, O. Picard, D. Zagury, P. Sarin, R. Gallo, P. Naylor, & A. Goldstein. HGP-30, a synthetic analogue of human immunodeficiency virus p17, is a target for cytotoxic lymphocytes in HIV-infected individuals. *Proc Natl Acad Sci* **87**:7045–7049, 1990. This epitope serves as a B cell epitope as well as an HLA-A2 T-cell epitope. The peptide is also called HGP-30.

[Addo (2001)] M. M. Addo, M. Altfeld, E. S. Rosenberg, & et al. The HIV-1 regulatory proteins Tat and Rev are freqently targeted by cytotoxic T lymphocytes (CTL) derived from HIV infected individuals. *Proc.Natl.Acad.Sci.* **98**(4):1781–1786, 2001.

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diversity to an immunodominant epitope was suggested to facilitate immune escape. gp41 epitope: ERYLKDQQL. An HLA B14 restricted RT epitope from this individual used Vα21 and Vβ14, showing use of these genes was not a feature of all HLA B14 restricted clones from this individual. RT epitope: AIYLALQDSGLEVNIVTDSQYALGI.

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I molecule showed striking similarity among the CTL of each haplotype, expressing either V beta 8.1 or V beta 14. In contrast, the fine specificity is different between the distinct MHC class I molecules even for the lysis by the same CTL, as shown by reciprocal effects of the same substitutions. Thus, peptide fine specificity of a single TCR is influenced by changes in the class I MHC molecules presenting the Ag.

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